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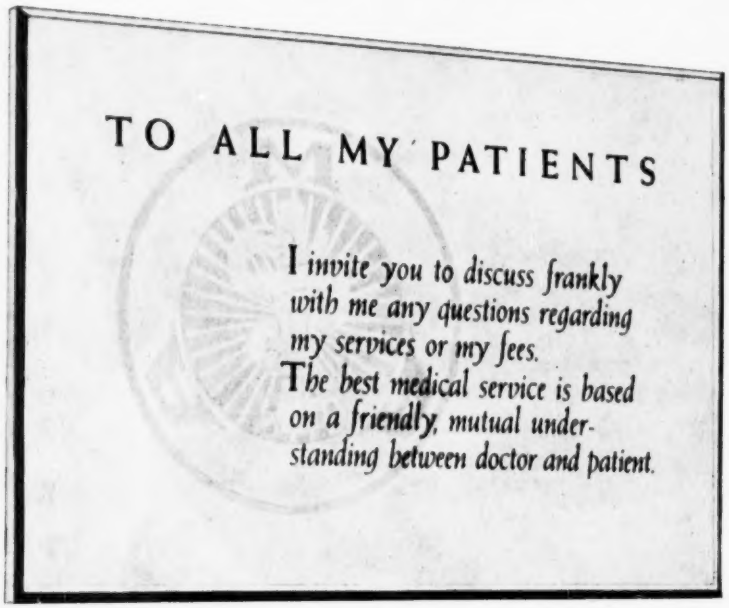
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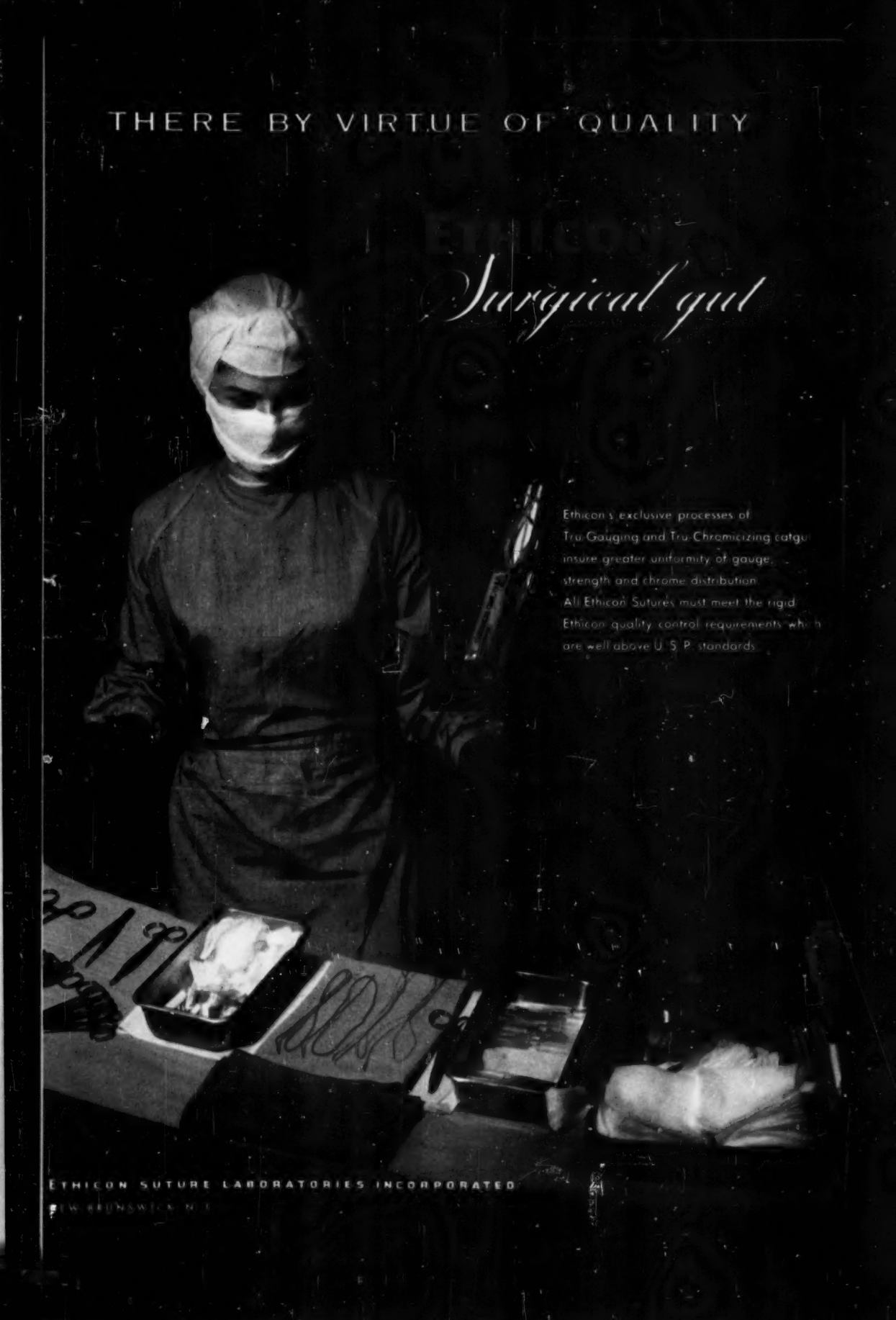
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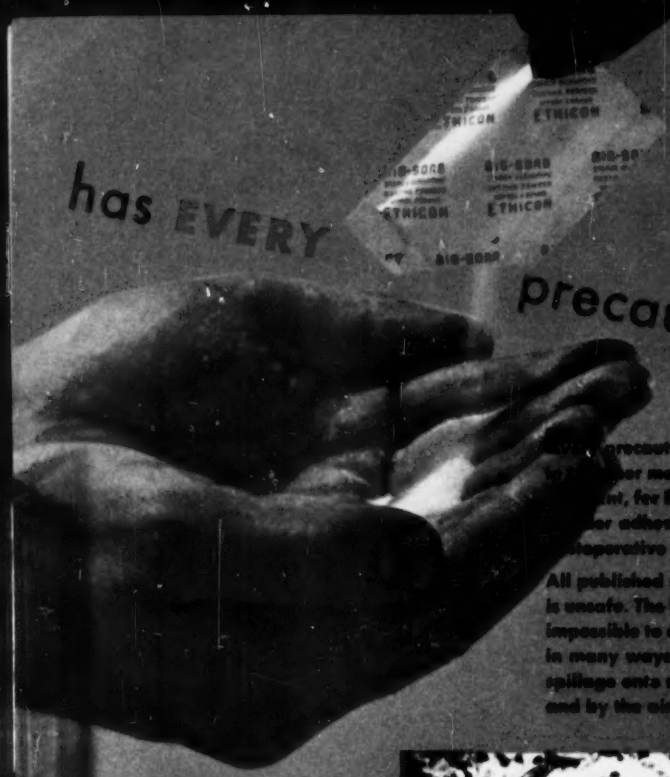

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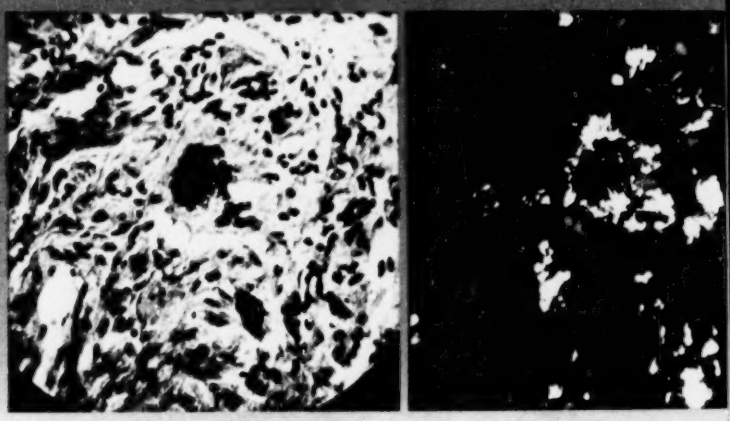

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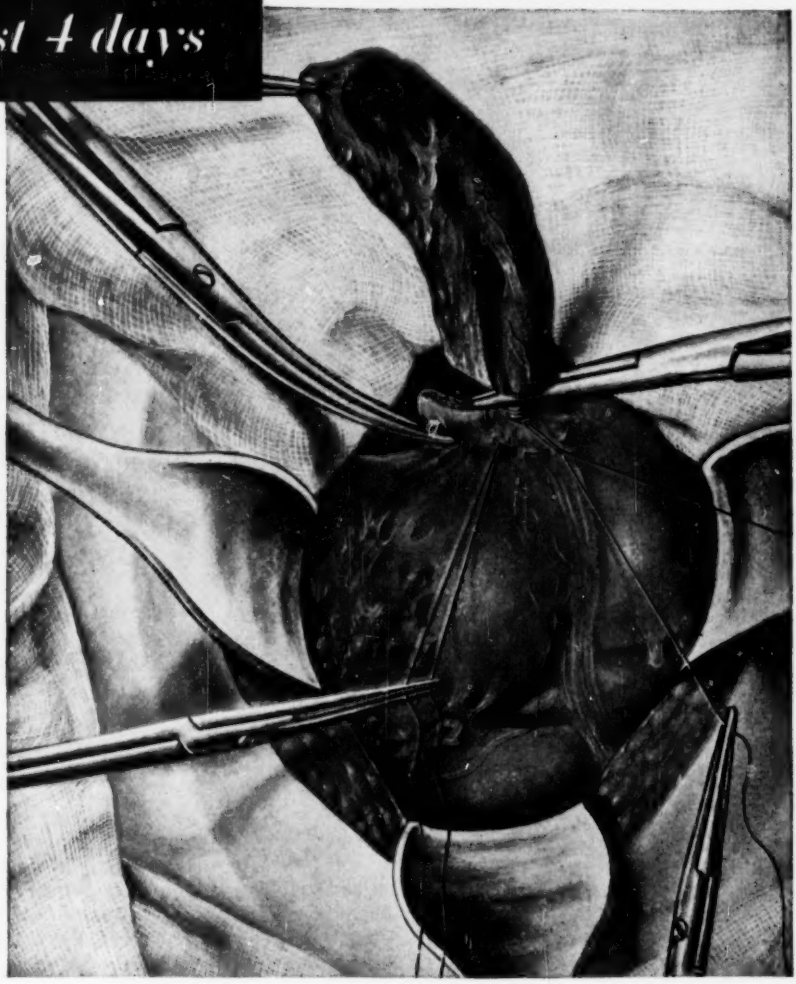

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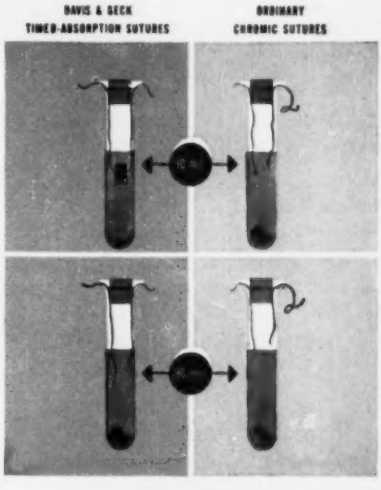

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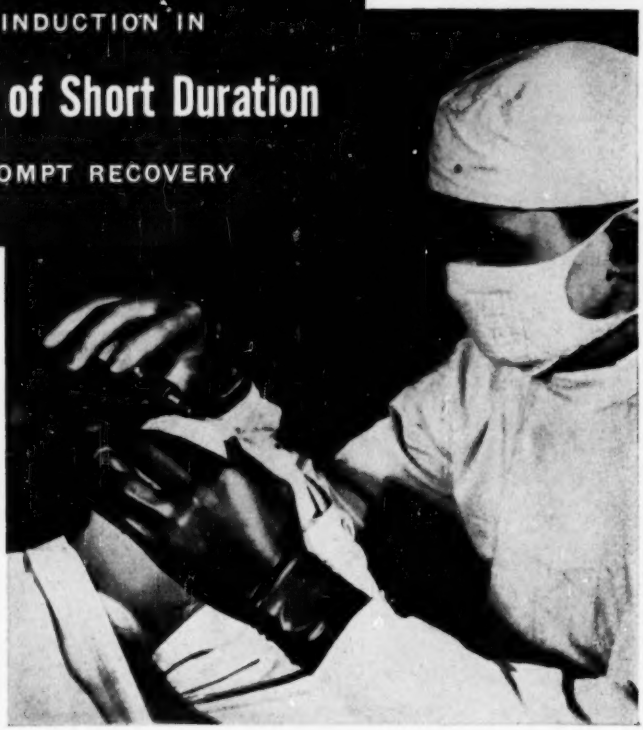

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VOLUME 64 JANUARY 1952 NUMBER 1

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Editorials

PROBLEMS OF HOMOLOGOUS SERUM JAUNDICE AFTER PLASMA TRANSFUSION

THE INCIDENCE of homologous serum jaundice after transfusions with pooled plasma is sufficiently high (5-15%) that many have abandoned its use save for the emergency treatment of shock. Although this decision is justified on the basis of clinical experience, it is regrettable that such a conclusion is necessary because we have available no other noncellular protein agent that is as effective in the treatment of shock or in the rapid restoration of the plasma protein concentration of the hypoproteinemia of malnutrition. Moreover, plasma or its fractions are the only portions of blood that can be stored indefinitely; hence the problem arises as to the disposition of plasma currently being collected as this applies to both military and civil defense.

The infectious agent responsible for homologous serum jaundice is considered to be a virus. Because only a small amount of an infected plasma is necessary to produce the disease, one unit of infected plasma may contaminate a very large plasma pool. In terms of the carrier rate in subjects presenting themselves as blood donors, it is arithmetically probable that most plasma pools containing 150 donors are contaminated. It is also probable that 15 to 20% of plasma pools containing 20 to 25 donors each will contain the virus. Hence, small pools of plasma are recommended. The preparation of small pools is a laborious and expensive procedure, necessitated by the frequent sterilization and re-use of equipment. Small pools are also undesirable because such small volumes fail to dilute adequately any abnormally high isoagglutinin titer that may occur in a particular donor. Thus, it is clearly evident that some method must be found whereby blood or plasma may be rendered nonicterogenic without disturbing those qualities in plasma essential in the treatment of shock and malnutrition.

The incidence of homologous serum jaundice following blood transfusion is small, less than 1%. For this reason most attempts to inactivate the virus of homologous serum jaundice have been directed toward the more durable and versatile by-products of blood, especially plasma.

From the Department of Surgery of the University of Chicago.

Attempts at "sterilization" of plasma have included exposures to ultraviolet light, ionizing irradiation, and certain chemical agents. While these procedures will kill viruses if used in sufficient strength, they can also damage the proteins of plasma. Certain of the chemical agents have also proved to be too toxic for general use. Reports of homologous serum jaundice following transfusion of pooled plasma previously subjected to ultraviolet light irradiation are sufficient in number to question seriously that this procedure offers any protection as it is now used.

At the University of Chicago Blood Bank, we have had no known case of homologous serum jaundice that could be attributed to our own plasma. During the past nine years we have administered 13,490 units of our plasma to 960 patients. Each patient on the average was exposed to 48 donors. During the same time 28,549 units of blood were given to 7,893 patients, of whom 26 came down with the classical picture of the disease. Seventy-two per cent of the patients receiving plasma were followed from four to six months; 66% of the patients receiving blood were observed for similar periods. Of the plasma group, 22 patients received large volumes of plasma representing donor populations of 200 to 726. This group was followed for six months or longer and none developed detectable latent jaundice. The patient who received plasma from 726 donors suffered from hypoglobulinemia and had little or no detectable gamma globulin. This patient presumably was susceptible to the disease. This series of 22 patients alone is sufficient to suggest strongly that our plasma is nonicterogenic, and, of course, simply augments the experience with the remaining 928 patients. The disparity of our results with those of all other reports is more clearly evident when one realizes that, save for our experience, all others have reported a much greater incidence of homologous serum jaundice following transfusion of pooled plasma than when only blood is given. While we have recognized homologous serum jaundice following blood transfusion in 26 patients and were forced to discontinue the administration of surplus lyophilized war plasma because of the high incidence of this disease, following its use, we have failed to recognize homologous serum jaundice following transfusion with our own plasma. What, then, is the reason for our good fortune with our own plasma?

From the beginning of our blood bank in 1942, all our plasma has been stored three months or longer in the liquid state at room temperature ranging between 78 and 96 F. No preservatives, including glucose, have been added. An analysis of the survival characteristics of viruses discloses that this method of storage is the most likely explanation of our apparent fortunate experience with pooled plasma. Viruses are said to "die out" when stored in a liquid, cell-free state for prolonged periods of time at room temperature. Lyophilized and/or frozen, most viruses survive for remarkably long periods. The latter methods are, in effect, suspended animation. In order to sustain a virus for study, most virologists have resorted to lyophilization or deep-freeze storage. Some agents are fairly resistant to refrigeration temperatures, but none is known to withstand prolonged room temperature storage when in a liquid cell-free state. This is true of such common agents as the viruses of rabies, smallpox, mumps, and influenza, and is true also for all other agents about which survival data are available. It appears to be common knowledge among virologists that a viral agent that may be stable for years in the

lyophilized or deep-frozen states rapidly becomes inactivated on standing in a liquid, cell-free state, although in the lyophilized state many of these agents withstand room-temperature storage very well.

If these observations of the virologists can be accepted as established facts, need it longer be surprising, then, that plasma containing the virus of homologous serum jaundice remains infectious for months to years when it has been stored in the lyophilized or frozen states? Indeed, if such plasmas did not produce homologous serum jaundice in some patients, there would probably be reason to question the viral nature of the pathogenic agent responsible for homologous serum jaundice, so generally do viruses respond to the manner in which they are stored. Likewise, there would also be reason to question the viral nature of the infective agent of homologous serum jaundice, if it did not "die out" on prolonged room-temperature storage in a cell-free, liquid state. Our data suggest that the virus of homologous serum jaundice behaves as other agents and that it loses its infectivity when stored for three to six months in the liquid cell-free state of plasma.

Is plasma stored in a liquid state of room temperature suitable in the treatment of shock and as a nutritive agent? Our own experience suggests that it is, even when stored for longer than one year. Reactions are rare (0.5%), and no fatalities have occurred. In fact, plasma stored under these conditions appears useful up to three years. Undoubtedly, there are changes in its physicochemical nature, but regardless of how pronounced these changes may prove to be in the laboratory, it seems doubtful if they are sufficient to alter the clinical response so far as the therapeutic use of such plasma in shock or malnutrition is concerned. Perhaps such plasma should be considered as a substitute, a substitute of the real thing, thereby differing from the synthetics. Time will tell.

Should all plasma be stored three to six months in a liquid form before it is administered or lyophilized? Although our own data support this view, such a move should not be undertaken until appropriate agencies can perform the critical experiment that will prove or disprove our observations. This entails the administration to human volunteers of plasma that is known to be contaminated with the virus, after storing such plasma at room temperature and for different time intervals. Before advocating its general use, it is also necessary to know more of the physiochemical and biochemical changes that occur in plasma stored under these conditions. Perhaps, by storing plasma at higher temperatures (45 to 55 C.), the viral agent might become inactive in a few days and thereafter lyophilization could safely be carried out.

Since all efforts thus far to render pooled plasma free of the virus of homologous serum jaundice have failed, should we continue the procedures of lyophilizing, deep freezing or refrigerating of plasma which still contains the virus, when it is so well established that these procedures favor the preservation of viral activity? Evidence more clearly condemns lyophilization and deep freezing than refrigeration; yet all three of these methods of storage must be carefully scrutinized, weighing risk against the benefits they offer, until it can be established that by some means plasma can be sterilized. Our own plasma data and the data of others regarding

the characteristics of virus survival in general correlate sufficiently well to encourage us in the belief that the serious problem of homologous serum jaundice can be solved in a simple and effective manner that takes into account those principles which govern the viability of viruses and which, at the same time, preserve the stability of the proteins of plasma. Stated more simply, it appears that liquid plasma will withstand room-temperature storage better than will viruses. The thermolability feature of viruses stored in a liquid, cell-free state merits clinical and laboratory investigation, for if such storing is successful in eradicating the virus of homologous serum jaundice, plasma could be used as a safe and inexpensive therapeutic agent.

J. GARROTT ALLEN, M.D.

TERRAMYCIN IN TREATMENT OF PERITONITIS

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THE FUNDAMENTAL principles of treatment of acute secondary peritonitis consist of immediate extirpation of the focus of infection whenever possible and "walling off" of the infectious process by host defenses. The use of potent antimicrobial agents in the regimen of supportive therapy has tipped the balance of forces in favor of the defense mechanisms by providing means for direct attack on the offending bacteria.

Sulfonamides, the first of the modern antimicrobial drugs, were shown to influence favorably early spreading but not localizing or localized peritonitis of fecal origin.[1] Penicillin, initially considered without influence on severe mixed infections, was demonstrated to be effective in peritonitis in the experimental animal and in patients when used in large doses.[2] Streptomycin also was shown to influence the outcome of human peritonitis.[3] Danger of untoward effects peculiar to earlier preparations and the threat of persisting infection with drug-resistant organisms restrained acceptance of this drug as a singly effective agent in peritonitis. Pure streptomycin with penicillin has gained wide popularity. These two drugs in combination affect the bacterial spectrum which commonly causes acute secondary fecal peritonitis. Aureomycin and terramycin have broad antibacterial spectra and have

---

From the Surgical Research Unit and Surgical Service, Brooke Army Hospital, Fort Sam Houston, Texas.

1. Ravdin, I. S.; Rhoades, J. E., and Lockwood, J. S.: The Use of Sulfonamide in the Treatment of Peritonitis Associated with Appendicitis, Ann. Surg. **111**:53, 1940.

2. Crile, G., Jr.: Peritonitis in Appendiceal Origin Treated with Massive Doses of Penicillin: Report of 50 Cases, Surg., Gynec. & Obst. **83**:150, 1946. Fauley, G. B.; Duggan, T. L.; Stormont, R. T., and Pfeiffer, C. C.: The Use of Penicillin in the Treatment of Peritonitis: Experimental Study, J. A. M. A. **126**:1132 (Dec. 30) 1944.

3. (*a*) Keefer, C. S., and Hewitt, W. L.: The Therapeutic Value of Streptomycin: A Study of 3000 Cases, Ann Arbor, Mich., Edwards Brothers Inc., 1948, p. 101. (*b*) Pulaski, E. J.; Seeley, S. F., and Matthews, C. S.: Streptomycin in Surgical Infections: IV. Peritonitis, Surgery **22**:889, 1947. (*c*) Pulaski, E. J.; Voorhees, A. B., and Seeley, S. F.: Further Experiences with Streptomycin Therapy in Peritonitis, Ann. Surg. **130**:242, 1949.

been shown to be effective drugs for peritonitis when used alone in both animals and man.[4]

The purpose of this communication is to confirm and extend our earlier report indicating that terramycin showed considerable promise in the treatment of peritonitis.

CLINICAL MATERIAL

Forty-seven patients were treated at Brooke Army Hospital and 21 at Tokyo Army Hospital. The two series of patients differ greatly as to etiology of the peritonitis, previous antibiotic therapy, and time of onset before terramycin treatment was instituted. Twenty-eight of the patients at Brooke Army Hospital had peritonitis of appendical origin. The remaining 19 patients constitute a heterogenous group which comprises six patients with pelvic inflammatory disease, four with gangrene of the bowel, three with perforated peptic ulcer, and one each with gunshot wound of the abdomen, knife wound of the abdomen, perforated carcinoma of the stomach, perforated carcinoma of the colon, perforated sigmoid diverticulum, and unknown etiological condition. All but three of the 21 Tokyo patients had peritonitis secondary to gunshot wounds of the abdomen, the three exceptions having appendicitis, a perforated peptic ulcer, and volvulus.

Terramycin was the initial antibiotic employed in 31 of the 47 Brooke patients. Fourteen patients received penicillin and streptomycin for an average of five days, one patient received penicillin alone for 11 days, and another was given aureomycin for three days and chloramphenicol for five days before terramycin therapy was instituted. In all of these the previous antibiotics had failed to bring the disease process under control. When terramycin was used initially, the patients in the Brooke series received antibiotic therapy within 24 to 48 hours after the onset of the disease. At the time of our mission in the Far East patients did not reach the Tokyo Army Hospital for an average of eight days after injury. Emergency surgery, including suture of the small bowel and colostomy, was performed in the forward areas. The routine antibiotic treatment for perforation of the intestinal tract consisted in the combined use of penicillin and streptomycin. The Tokyo patients had received treatment with this antibiotic combination for one to 26 days. The average time of treatment under this regimen was eight days in 17 instances of gunshot wounds of the abdomen. One patient with a traumatic abdominal wound had received no previous antibiotic therapy, and one other had been given six days'

4. Pulaski, E. J.; Shaeffer, J. R.; Artz, C. P., and Baker, H. J.: Studies on the Use of Terramycin in Experimental and Clinical Peritonitis, Surgical Forum, American College of Surgeons, Philadelphia, W. B. Saunders Company, 1951, p. 119. Rutenburg, A. M.; Schweinburg, F. B., and Fine, J.: Clinical Experiences with Aureomycin in Surgical Infections, Ann. Surg. **133**:344, 1951. Wright, L. T.; Metzger, W. I.; Shapero, E. B.; Carter, S. J.; Schreiber, H., and Parker, J. W.: Treatment of Acute Peritonitis with Aureomycin, Am. J. Surg. **78**:15, 1949. Wright, L. T., and Prigot, A.: Aureomycin as an Aid in Abdominal Surgery, Ann. Surg. **133**:364, 1951. Wright, L. T.; Schreiber, H.; Metzger, W. I., and Parker, J. W.: An Evaluation of Aureomycin Therapy in Peritonitis: A Report of 235 Consecutive Cases, Surg., Gynec. & Obst. **92**:661, 1951. Yeager, G. H.; Lynn, W. D., and Barnes, T. G.: Treatment of Peritonitis of Appendiceal Origin with Aureomycin, South. Surg. **16**:1192, 1950. Yeager, G. H.; Mansberger, A. R., Jr.; Thomas, C. D. Jr., and Barnes, T. G.: Terramycin in Peritonitis: Experimental and Clinical, Ann. New York Acad. Sc. **53**:319, 1950.

therapy with penicillin alone. One patient with appendicitis and one with a perforated peptic ulcer were treated with terramycin from the start.

At Brooke Army Hospital the patients ranged from 20 to 78 years, the average being 34 years. All the patients treated at Tokyo Army Hospital were healthy soldiers prior to injury, their ages ranging from 18 to 30 years and the average being 21 years.

A uniform dosage regimen was employed. This consisted of 1 gm. of terramycin intravenously every 12 hours for two to four days and then, as soon as oral medication could be tolerated, 0.5 gm. by mouth every six hours for 8 to 10 days.

METHOD OF EVALUATION

All patients were studied in a manner similar to that which was used in the evaluation of streptomycin.[5] Peritonitis was again classified as spreading, localizing, and localized. The disease process was termed as spreading only when normal forces of localization were not apparent and the clinical picture was that of an overwhelming peritoneal infection, as indicated by high fever, generalized abdominal tenderness, absence of peristalsis, marked abdominal distention, and leucocytosis. The term localized peritonitis was reserved for those instances in which definite abscess formation had taken place. In this group, patients had temperatures from 101 to 104 F., but distention was usually not a prominent feature and peristalsis was often present. The term "localizing peritonitis" was reserved for cases in which signs of localization were apparent on repeated examination but definite abscess formation was not evident. All the patients in this classification had a temperature of 101 F. or more. Abdominal distention was almost always present, although some low-grade peristalsis could frequently be heard.

The criteria for evaluation of the chemotherapeutic response were not rigid. Particular attention was paid to the time of defervescence, the return of peristalsis, and the occurrence of complications, such as abscess formation necessitating surgical drainage. In every instance an attempt was made to establish the part played by the antibiotic in the over-all therapy of the patient. The result was classified as excellent when the temperature fell to normal, peristalsis returned, and abdominal tenderness receded in 48 to 72 hours. More gradual improvement was termed a good result. A doubtful response was one in which beneficial results could not be definitely ascribed to the antibiotic. Sometimes surgical drainage appeared to be the most important factor in effecting a recovery. It thus became necessary on several occasions to list the role of the antibiotic as doubtful even though the final result achieved could be considered excellent or good.

ANALYSIS OF RESULTS

The accompanying table shows that the largest number of excellent responses was achieved in the group of cases of spreading peritonitis and that the incidence of such dramatic results declined in the less virulent infections (localizing and localized). Of the 32 patients with spreading peritonitis, results were excellent in 17, good in 8, doubtful in 1, and poor in 6. Four of the five patients with spreading appendical peritonitis with excellent responses did not require surgery. The one patient with a poor response in this group represents one of the two who died in

5. Pulaski, Voorhees and Seeley.[3c]

this study. He was a 61-year-old white man who one month before his death was hospitalized with spreading peritonitis of unknown origin. His initial response to penicillin and streptomycin was satisfactory; however, 15 days after his admission an abscess extending over both lower quadrants of the abdomen became evident, and this was drained through a midline incision. In the ensuing 30 days the drainage gradually subsided and the wound was healing by secondary intention. On the 30th postoperative day the patient's abdomen became distended, dyspnea was marked, and a previously normal temperature rose to 105 F. Intensive supportive therapy and intravenous administration of terramycin, 1 gm. twice a day, failed to effect any improvement. The patient died six days later. Postmortem examination revealed the presence of a perforated appendix, an early spreading peritonitis, and purulent pericarditis. The latter was apparently the major cause of the patient's death.

Results in Sixty-Eight Cases of Peritonitis Treated with Terramycin

Type	Total No. of Cases	Response			
		Excellent	Good	Doubtful	Poor
Spreading	32	17	8	1	6
Appendical	6	5	..	..	1*
Gunshot wound	14	5	4	1	4
Perforated gastrointestinal tract	6	3	3	..	..
Internal obstruction with gangrene	4	2	1	..	1*
Others	2	2	..	..	..
Localizing	18	5	12	1	..
Appendical	15	5	10	..	..
Gunshot wound	2	..	1	1	..
Perforated peptic ulcer	1	..	1	..	..
Localized	12	3	5	4	..
Appendical	8	1	4	3	..
Gunshot wound	4	2	1	1	..
Pelvic inflammatory disease	6	1	4	1	..

* Death.

The second death occurred in a 78-year-old white man with peritonitis secondary to a mechanical intestinal obstruction of the ileum with gangrene. He died seven days after operation and the institution of intravenous terramycin therapy. Autopsy revealed a resolving peritoneal infection and thrombosis of the right middle cerebral artery. The cause of death was probably not related to the intraperitoneal disease.

Four patients with spreading peritonitis secondary to gunshot wounds of the abdomen who had failed to respond to previously given penicillin and streptomycin also failed to show evidence of improvement after three days of intravenous terramycin therapy. In every instance, terramycin-resistant organisms were cultured from the operative wounds. In three of the patients the wound organisms were sensitive to chloramphenicol and clinical improvement was coincident with the intravenous administration of this drug. In the fourth patient an Escherichia coli organism resistant to terramycin was found in both the blood stream and the wound drainage. An immediate response followed the intravenous administration of streptomycin, 1 gm. twice daily.

Eighteen patients with localizing peritonitis were treated. The response was excellent in 5, good in 12 and doubtful in 1. In the appendical group, two of the patients with an excellent response recovered uneventfully without operation. In

these, abscess formation was evident at one time, but rapid resolution occurred under continued intensive antibiotic management. In the three others, appendectomies were performed. Good responses were achieved in eight patients with appendectomies, in one with incision and drainage of abscess, and in one with nonoperative management.

In the localized group 12 patients were treated. Three excellent, five good, and four doubtful responses were observed. The patients with doubtful responses all recovered uneventfully, but in each instance it appeared that surgical incision and drainage was primarily responsible for recovery.

The six patients with pelvic inflammatory disease had acute pelvic peritonitis superimposed on a chronic pelvic inflammatory proce.s. In all but one of these previous penicillin and streptomycin therapy had failed.

UNTOWARD REACTIONS

Two patients experienced nausea and vomiting when the drug was administered intravenously, and in one chemical phlebitis developed at the site of injection. One patient had nausea and mild diarrhea, which spontaneously subsided even though oral medication of the drug was continued. Two other patients had mild nausea and vomiting, which was relieved when the capsules were given with milk. We are inclined to attribute the low incidence of nausea and vomiting after oral medication to the routine administration of the drug with milk.

COMMENT

Terramycin is established as a most useful and potent antibacterial agent. Its wide antimicrobial spectrum and good penetrability into peritoneal exudate recommend it as an agent with potential usefulness in the treatment of peritonitis.[6] Experimental studies in animals and preliminary trial in patients have yielded encouraging results. The present report confirms and amplifies these findings.

Because of the many factors involved in the successful management of a complex disease like peritonitis, the comparative efficacy of various antibiotics in man is difficult to establish. Wide experience with the combined use of penicillin and streptomycin has indicated that this antibiotic combination has real merit in the treatment of peritonitis. Our data show that terramycin, like aureomycin, is a singly effective, superior antibiotic in the treatment of peritonitis and that a good result can frequently be obtained with this drug when penicillin and streptomycin have failed. It thus has great usefulness both as a primary therapeutic agent and as an alternate antibiotic. The growing antibiotic armamentarium gives the surgeon of today several antimicrobial agents when one or the other drug fails to produce prompt improvement in the treatment of peritonitis.

SUMMARY

Sixty-eight patients with peritonitis were treated with terramycin. The over-all results were gratifying. Two deaths occurred, and one of these could be explained on the basis of concomitant disease rather than of antibiotic failure. In four patients the disease process failed to respond on adequate trials of intravenous terramycin therapy but recovery followed the administration of an alternate antibiotic.

6. Pulaski, E. J.; Artz, C. P., and Reiss, E.: Terramycin in Surgical Infections, J. A. M. A., to be published.

LUNG CANCER

Angiocardiographic Findings in One Hundred Consecutive Proved Cases

ISRAEL STEINBERG, M.D.
AND
CHARLES T. DOTTER, M.D.
NEW YORK

CURRENT vital statistics emphasize the medical importance of any means of gaining information about lung cancer. Through its unique ability to delineate major intrathoracic vascular structures, angiocardiography constitutes a useful addition to the diagnostic methods employed in the study of carcinoma of the lung in the living patient.[1] The chief function of all clinical and laboratory procedures, including angiocardiography, is to demonstrate the nature and extent of pathological change within the patient. The accumulation of such information is a prerequisite to evaluation from a diagnostic, prognostic, and therapeutic viewpoint. The survey reported here indicated that angiocardiographically demonstrable vascular change occurs in 87% of cases of lung cancer. In 43% of the cases studied there is vascular evidence indicating probable inoperability of the lesion.

METHOD AND RESULTS

Case material for the present report consisted of 100 consecutive microscopically proved instances of carcinoma of the lung studied by angiocardiography. The first 53 of these cases were the subject of a previous report.[1d] The angiocardiograms, conventional roentgenograms and clinical, surgical and pathological records were assembled and reviewed in an effort to evaluate in retrospect the possible usefulness of contrast cardiovascular visualization. In order to simplify description of the pathologic changes encountered, each lesion was classified into the most appropriate of five groups depending on the vascular changes demonstrated. These groups consisted of cases in which (1) no vascular changes were demonstrated, (2) the

From the Departments of Radiology and Medicine of the New York Hospital—Cornell Medical Center.

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1. (*a*) Steinberg, I., and Robb, G. P.: Mediastinal and Hilar Angiography in Pulmonary Disease: A Preliminary Report, Am. Rev. Tuberc. **38**:557-569, 1938. (*b*) Steinberg, I.; Dotter, C. T., and Andrus, W. D.: Angiocardiography in Thoracic Surgery, Surg., Gynec. & Obst. **90**:45-59, 1950. (*c*) Dotter, C. T., and Steinberg, I.: Angiocardiography, New York, Paul B. Hoeber Inc., 1951. (*d*) Dotter, C. T.; Steinberg, I., and Holman, C. W.: Lung Cancer Operability: Angiocardiographic Study of 53 Consecutive Proved Cases of Lung Cancer, Am. J. Roentgenol. **64**:222-238, 1950.

superior vena cava or its tributaries was involved, (3) the right or left pulmonary artery was involved, (4) segmental pulmonary arteries only were involved, and (5) the pericardium was involved. When great vessels were affected by tumor, certain findings were nonspecific, others suggested malignant changes, while still other changes were regarded as conclusive evidence of invasiveness. These vascular deformities (arranged in the order of increasingly evident invasiveness) were (*a*) nonspecific vascular displacement, (*b*) external pressure defects without demonstrable stenosis of the involved vessel, (*c*) vascular stenosis and occlusion, and (*d*) polypoid intraluminal vascular invasion. It is apparent from a statistical point of view that complete occlusion of a vessel constitutes more impressive evidence of a malignant process than does a partial stenosis or a simple displacement without luminal narrowing. In the assessment of individual cases, however, didactic con-

Vascular Changes Revealed by Angiocardiography in Lung Cancer (Cases Classified According to Principal Lesion)

	Per Cent of Cases
1. No vascular changes with	
(*a*) no parenchymal disease on x-ray	2
(*b*) peripheral lung cancer	8
(*c*) peripheral lung cancer with fluid	1
(*d*) hilar or mediastinal cancer	2
Total	13
2. Involvement of superior vena cava system	
Axillary vein	2
Subclavian vein	4
Innominate vein	2
Superior vena cava (polypoid invasion, 2)	9
Total	17
3. Major pulmonary artery involvement	
Right	4
Left	21
Total	25
4. Segmental pulmonary artery involvement	44
5. Pericardial invasion	1
All cases	100

clusions are usually unwarranted, since non-neoplastic lesions may produce a wide variety of vascular abnormalities and since malignant tumors frequently fail to produce characteristic changes on angiocardiography. The angiocardiographic findings in this series of 100 cases of lung cancer are summarized in the table. Five of the 100 patients were female.

Normal Vascular Structures.—In 13 of the 100 cases there was no discernible evidence of vascular distortion, displacement, or narrowing. There was no demonstrable change in the chest roentgenogram in two of these cases. In one, the diagnosis was established by cytological examination of the sputum. Autopsy, following death due to an unrelated cause, revealed a carcinoma "in situ" of the bronchus. The case is reported elsewhere.[2] In the other case, the roentgenogram of the chest was negative and the lesion, suspected because of hemoptysis and cytological evidence of a malignant process in the sputum, was located bronchoscopically. Since both lesions were situated entirely within but not obstructing a bronchus, neither roentgenography nor angiocardiography was of diagnostic value.

2. Papanicolaou, G. N., and Koprowska, I.: Pulmonary Carcinoma in Situ of the Right Lower Bronchus, Cancer **4**:141-146, 1951.

In eight cases, peripheral carcinoma of the lung produced no angiocardiographically demonstrable change in the pulmonary segmental arteries (Fig. 1). It is recognized that minor vascular changes probably existed but could not be identified by the gross method of study employed. Application of microangiographic technics to the living patient may further facilitate the differential diagnosis of pulmonary parenchymal densities. Pleural effusion was the only roentgenographic evidence of lung cancer in one case in which angiocardiography showed no vascular change, and a similar situation was present in one case of superior sulcus tumor. The nonvascular nature of hilar or mediastinal tumor masses was revealed by angiocardiography in two cases. Here, although vascular deformity was not shown, angiocardiography was of "negative" value in indicating the presence and location of abnormal nonvascular structures.

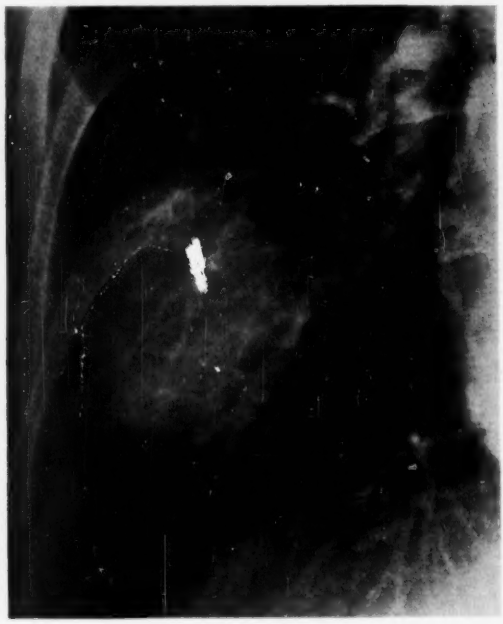


Fig. 1.—Peripheral lung cancer—no vascular abnormality. An asymptomatic 58-year-old electrician was found to have a right lower lobe tumor on routine x-ray examination of the chest. Angiocardiography (enlarged view right lower lobe) showed normal vascular pattern in region of tumor. Lobectomy specimen contained oat-cell carcinoma. Recurrence and death followed within 18 months.

Involvement of the Superior Vena Cava System.—The thin-walled superior vena cava and its tributaries readily reflect the presence of adjacent mediastinal, subclavian or axillary disease.[3] Although thrombosis and aneurysm are frequent causes of superior vena cava obstruction and displacement, tumors of the medias-

3. Roberts, D. J., Jr.: Dotter, C. T., and Steinberg, I.: Superior Vena Cava and Innominate Veins: Angiocardiographic Study, Am. J. Roentgenol. **66**:341-352, 1951.

tinum, primary or secondary, are the most frequent causes. Since the lymphatics of the right lung drain by way of the right parabronchial and paratracheal lymph nodes, carcinoma of the right lung is often associated with superior vena cava deformity. In this series, 17 cases showed deformities of the superior vena cava system, including the superior vena cava (nine cases), the innominate (two cases), the axillary (two cases), or the subclavian veins (four cases). In 15 cases, abnormalities of the superior vena cava system were associated with carcinoma of the right lung while there were similar changes in only two cases when the left lung was involved. Superior vena cava obstruction may be the result of thrombosis, external pressure, or invasion of the vessel by neoplasm. In two cases, polypoid intraluminal tumor masses were demonstrated (Fig. 2). A ragged filling defect is produced which must and usually can be distinguished from the change resulting

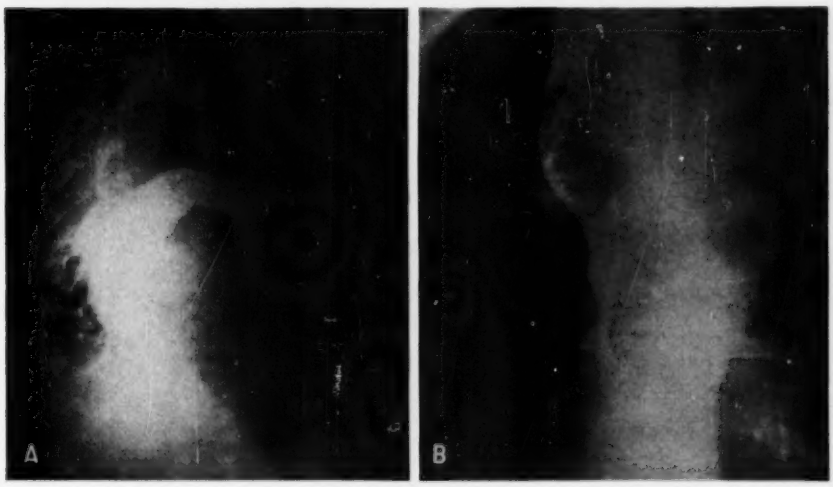


Fig. 2.—Polypoid invasion of superior vena cava. *A*, a 46-year-old man had chronic cough, weight loss, edema of face and arms and cyanosis of six months' duration. Bronchoscopic biopsy showed epidermoid carcinoma involving the carina. Angiocardiography revealed a polypoid filling defect of the superior vena cava. The right upper lobe was atelectatic, and the ascending branch of the right pulmonary artery was occluded. Operation was not offered because of the angiocardiographic evidence of inoperability. Death occurred within one year. *B*, a 50-year-old truck driver with a four-week history of swelling of the face, neck, arms, and upper chest and a 5 lb. (2.3 kg.) weight loss had a wheeze in the right chest on auscultation. Angiocardiography revealed a polypoid deformity of the superior vena cava. Later angiocardiographic films showed stenosis of the right pulmonary artery at its bifurcation. Operation was not offered because of the above findings and the presence of secondary carcinoma of the skin.

from external pressure. Carcinoma of the upper lobe, particularly the superior sulcus tumor, may traverse the thoracic wall to cause stenosis or obstruction of the subclavian vein (present in three cases), thereby offering strong evidence of inoperability (Fig. 3). When stenosis or occlusion of the superior vena cava system occurs, it is readily recognized and located by angiocardiography. The filling of collateral channels is often striking. In such cases, if it is desired to examine the pulmonary arteries for evidence of an underlying cancer rather than study the site

of block itself, it is usually necessary to modify the technic of angiocardiography (for example, by utilizing a lower extremity vein for the injection).[4]

Major Pulmonary Arteries.—Hilar and mediastinal extension of lung cancer often produces involvement of the right or left main branch of the pulmonary artery. As observed in this series of cases, the degree and nature of involvement varied widely and included (1) simple displacement due to atelectasis, (2) distortion and narrowing of the lumen by means of external pressure and (3) severe, sharply outlined, irregular constriction produced by surrounding tumor. Recognition of the latter condition can be made with certainty only when the affected vessel is sufficiently well filled to outline the stenosis clearly. Poor contrast within a vessel may result from locally decreased pulmonary arterial flow in the absence of vascular occlusion. Disease processes other than cancer of the lung may produce stenosis or occlusion of major branches of the pulmonary artery and simulate the effects of

Fig. 3.—Occlusion, subclavian vein. A 54-year-old man with right chest pain radiating to the shoulder had swelling of face, neck, chest, and arms of only three weeks' duration. An angiocardiogram revealed sharp occlusion of the right subclavian vein. Numerous shoulder girdle and neck vein collaterals were shown. Bronchoscopic biopsy revealed epidermoid carcinoma. Death ensued several months later.

cancer. Tuberculous hilar lymphadenopathy and pulmonary actinomycosis are examples.[1c]

Sharp irregular stenosis of one of the major pulmonary arteries is sufficiently common in the presence of lung cancer and sufficiently rare in its absence to constitute presumptive evidence of the disease. The finding is usually ominous from the prognostic point of view, particularly if the stenosis is close to the bifurcation of the pulmonary artery. Stenosis or occlusion of the left pulmonary artery within 1.5 cm. of its origin and of the right pulmonary artery proximal to its bifurcation (Fig. 4) indicates that the mediastinum is probably involved. Although severe grades of stenosis are commonly encountered, complete occlusion is rare and usually

4. Jacobs, H. J.; Levy, L., II; Chastant, H., and Strauss, H.: Angiocardiography in Obstruction of the Superior Vena Cava, J. A. M. A. **147**:1051-1052 (Nov. 10) 1951.

can be ruled out in a given case by the demonstration of filling of the segmental pulmonary arteries distal to the point of narrowing. Of the 100 cases of proved lung cancer reported here, 25 showed evidence of involvement by tumor of one of the two major branches of the pulmonary artery.

Although in this series the incidence of cancer of the right lung (53%) approximated that of cancer of the left lung (47%), the left pulmonary artery was far more commonly affected (21%), while the right pulmonary artery was involved in only 4% of the cases reviewed. This apparent discrepancy is probably due to the fact that the major part of the right pulmonary artery lies within the central mediastinum while the left pulmonary artery enters the left lung directly after it takes origin. The demonstration of narrowing of the left pulmonary artery should include study in the left anterior oblique projection, since only in this view can the amount

Fig. 4.—Complete occlusion of right pulmonary artery, proximal to bifurcation. A 59-year-old subway signal man with a seven months' history of cough, purulent expectoration, and wheezing, experienced sudden right chest pain. Angiocardiography revealed occlusion of the right pulmonary artery (arrow). The superior vena cava was widened, and the azygos vein was opacified. Thoracotomy revealed an empyema, and a biopsy specimen of the right lower lobe showed bronchial carcinoma.

of normal vessel between stenosis and bifurcation be assessed, a point of prognostic significance. The right pulmonary artery can be adequately examined in frontal projection. Major pulmonary arterial involvement constitutes the most important although not the commonest angiocardiographic finding in carcinoma of the lung.

Segmental Pulmonary Arteries.—Angiocardiographic evidence of abnormality of the segmental pulmonary arteries is present in the majority of cases of radiographically demonstrable lung cancer. In 44 cases of this series, such changes represented the chief evidence of vascular deformity. A commonly encountered abnormality (28%) was that produced by atelectasis, a crowding together and poor

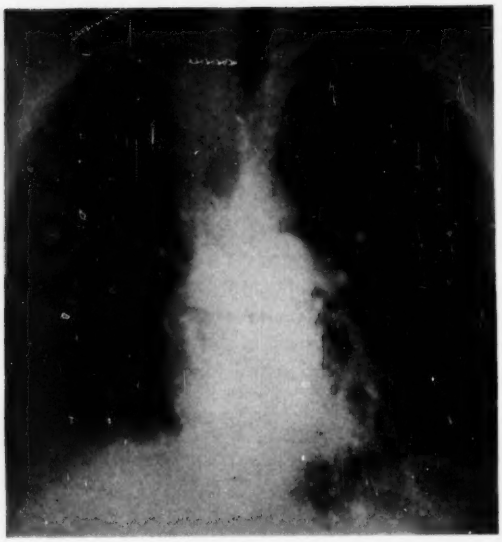


Fig. 5.—Stenosis, ascending branch of right pulmonary artery. A 60-year-old engineer complained of cough, hemoptysis, wheezing, and dyspnea of two months' duration. Angiocardiography showed stenosis of the ascending branch of the right pulmonary artery, with atelectasis of the right upper lobe. Pathologic examination after right pneumonectomy showed carcinoma of the right upper lobe bronchus which had extended into the azygos vein. Death ensued six months later.

Fig. 6.—Segmental pulmonary arterial changes, right upper lobe. A 46-year-old plumber complained of pain in neck, right shoulder, arms, and fingers of five months' duration. Angiocardiography revealed nonspecific displacement of one of the small segmental arteries by the expanding tumor. A specimen taken after right pneumonectomy showed a localized carcinoma of the lung.

filling of the affected segmental arteries (Fig. 5). The identification of atelectasis and its segmental localization is occasionally facilitated by angiocardiography, but the finding is by no means characteristic of carcinoma. Pleural effusion may cause minor nonspecific displacement of basilar pulmonary segmental arteries.

When centrally located tumor masses are present, there is usually poor filling of the segmental arteries peripheral to the area of tumor resulting in a condition loosely referred to as relative avascularity. In itself, this change is of little significance since it may result from bronchial obstruction or any of a variety of conditions causing local reduction in pulmonary blood flow.[1c] In areas of emphysema, the segmental arteries are usually widely separated and often poorly filled with contrast substance.

Peripheral neoplasms of the lung may not produce grossly demonstrable segmental arterial changes (Fig. 1) or they may displace adjacent vessels (Fig. 6). It is probable that careful study of the minor segmental vessels might result in the demonstration of changes characteristic of malignancy, but we were unable to identify such changes. Mere nonfilling need not represent neoplastic stenosis, while vascular displacement due to an expanding mass does not indicate whether the lesion is benign or malignant.[1b]

Pericardium.—In one case of this series, illustrated elsewhere,[1d] there was a localized thickening between the right atrium and the right lung. This was interpreted as evidence that invasion of the pericardium from a bronchoscopically proved carcinoma of the right middle lobe had occurred, a unique finding in our experience.

COMMENT

The information regarding vascular changes in lung cancer summarized above may be obtained from monographs and articles on the subject. The pathological changes in themselves are well known.[5] The chief contribution of angiocardiography to the study of lung cancer lies in the fact that such vascular alterations may now be studied in the living patient, prior to thoracotomy. Information gained from the examination of an individual patient thus is twofold in value, serving to add to the generally available knowledge of the disease and, more important from the patient's point of view, also aiding in the diagnostic and prognostic evaluation of the problem at hand.

Diagnosis is facilitated in that angiocardiography reveals vascular changes produced by cancer. While certain of these changes are nonspecific, they occasionally are sufficiently characteristic to allow a definite etiologic diagnosis. The demonstration of the vascular changes of atelectasis may augment, alter or confirm conventional roentgenologic findings, but it usually fails to identify the cause. When sharp, irregular stenosis or occlusion of a central pulmonary artery is shown, the evidence for malignant tumor increases markedly in significance. Since a variety of non-neoplastic conditions such as tuberculosis, Boeck's sarcoid, severe pulmonary fibrosis, actinomycosis, and other lesions may similarly cause stenosis of major vessels, angiocardiographic findings should be considered corroborative or supportive rather than conclusive evidence of the diagnosis. Angiocardiography constitutes a useful addition to the variety of diagnostic methods (radiography, bronchoscopy,

5. Fried, B. M.: Bronchiogenic Carcinoma and Adenoma of the Lung, Baltimore, Williams & Wilkins Company, 1948.

cytology) employed with so much success in cancer of the lung. Its value, unfortunately, has thus far been limited to those cases in which grossly recognizable disease was present. In no instance has angiocardiography been of diagnostic aid when the chest roentgenogram was entirely normal.

Prognosis in lung cancer is usually considered in terms of the expected survival period. In general, this is taken to mean that the prognosis is good when the lesion is operable and poor when it is not. Since radiation therapy deserves a place in the care of certain patients with carcinoma of the lung and since in other cases surgery does not, operability should not be considered as synonymous with prognosis. Pragmatically, angiocardiography is of great value in the preoperative assessment of operability of given lesions.

An inoperable lung cancer is defined here as one which cannot be resected without leaving behind grossly visible or palpable tumor. Any other definition of inoperability would be of less value to the surgeon at the time of exploration. As a result of a previous study,[1c,d] certain angiocardiographic findings in the presence of carcinoma of the lung are considered to be evidence of inoperability. These include (1) partial or complete occlusion by tumor of the left pulmonary artery within 1.5 cm. of its site of origin and partial or complete occlusion by tumor of the right pulmonary artery proximal to its point of bifurcation; (2) partial or complete occlusion of the great mediastinal veins due to tumor in the mediastinum (polypoid defects in the superior vena cava indicating the intraluminal growth of neoplasm have been observed); (3) the demonstration of mediastinal metastases by the contrast delineation of displacement and deformity of adjacent vascular structures (this consists simply of the demonstration of masses within the mediastinum through external pressure defects on vessels; the vascular changes in themselves are not diagnostic of malignant tumor tissue, but if the assumption is allowed that such masses are actually composed of the same tissue as a known peripheral cancer of the lung, it follows that mediastinal spread has occurred); (4) the demonstration of pericardial invasion by tumor (this consists of the demonstration of localized thickening of the pericardium in the absence of pleural disease in the vicinity; it was encountered in one case of this series).

Since non-neoplastic lesions may simulate the above changes, it is apparent that unsupported angiocardiographic findings should not be considered conclusive evidence that the patient is suffering from malignant disease beyond the limits of surgical resectability. The possibility of honest error in the "prognostic" evaluation of cancer of the lung by angiocardiography can never be excluded. It is apparent that contrast visualization will assist greatly in reaching a decision as to whether surgery is indicated or not. It is our belief that patients with obviously inoperable disease (as determined by all available methods) should be spared the discomfort of thoracotomy. The effectiveness of radiation therapy will thereby be increased, whether such therapy is designed for palliative or curative purposes. Angiocardiography may further be of service to the patient with lung cancer by indicating to the surgeon what he will encounter at thoracotomy and thus prevent protracted exploratory procedures. For example, when angiocardiography has shown the presence of probable mediastinal metastases the surgeon can direct his attention to the exact area immediately, abandoning the procedure if frozen section confirms the angiocardiographic diagnosis.

SUMMARY

A series of 100 patients with microscopically proved cancer of the lung was studied by angiocardiography. In 87% there was evidence of vascular abnormality as the result of tumor. Lesions could be grouped according to the presence and site of vascular abnormality as follows: superior vena cava system involved, 17%; right or left pulmonary artery involved, 25%; segmental pulmonary arteries involved, 44%; pericardium involved, 1%; no demonstrable vascular involvement, 13%. Forty-three per cent of the cases showed vascular deformities pointing toward a diagnosis of inoperability. Included were those with involvement of the major pulmonary arteries, the superior vena cava system, or the pericardium.

On correlation of these findings with clinical, operative and pathologic findings, it was possible to indicate how angiocardiography may play a significant role from the standpoint of diagnosis and the assessment of operability. It is predicted that in the study of certain types of carcinoma of the lung, the use of angiocardiography will become commonplace.

PARENTERAL NUTRITION WITH A SOLUTION CONTAINING ONE THOUSAND CALORIES PER LITER

CARL O. RICE, M.D.
J. H. STRICKLER, M.D.
AND
PAUL D. ERWIN, M.D.
MINNEAPOLIS

FOR YEARS it has been repeatedly mentioned in the medical literature that the problems of parenteral nutrition would be augmented if adequate calories could be provided [1] without overhydration of the patient. The work of Elman [1b] throughout the past few years has started an avalanche of studies pertaining to the value of electrolytes and parenteral nutrition for the patient who is unable to consume adequate food. His studies will go down, no doubt, in the annals of medical history as the beginning of one of the milestones in the advancement of the preoperative and postoperative care of the surgical patient.

In the earlier days of saline therapy the surgeon was not infrequently accused of having drowned the patient because of the use of too much fluid. It was soon learned that the offending factor was the use of excessive amounts of sodium chloride which caused a retention of water. This condition was rectified by a change to the use of glucose in distilled water, but the fear of excessive hydration lingered, and calories were not adequately provided.

Hypertonic solutions of glucose, as a means of providing more calories, offer disadvantages because of the local reactions which are produced in the vein, the renal glycosuria and diuresis [2] which so often result, and the adverse effect on the excretion of potassium. The studies of Weinstein indicate that invert sugar can be given intravenously at the rate of 1.5 gm. per kilogram per hour with an average loss of only 1.6 gm. of sugar per 100 cc. in the urine. The addition of alcohol to glucose and

This study has been conducted at the St. Barnabas Hospital, Minneapolis, as part of the teaching program for surgical residents from the University of Minnesota. Invaluable technical assistance has been rendered by Joyce English and Marian Thiele. Funds were provided in part by the Baxter Laboratories.

1. (*a*) Benditt, E. P., and others: The Dynamics of Protein Metabolism, J. Lab. & Clin. Med. **33**:257-268, 1948. (*b*) Elman, R.: Parenteral Alimentation in Surgery, New York, Paul B. Hoeber, Inc., 1947. (*c*) Pareira, M. D.; Probstein, J. G., and Somogyi, M.: The Influence of Varying Subcaloric Diets on Nitrogen Loss and Recovery Following Standardized Surgical Trauma, Surg., Gynec. & Obst. **92**:90-94, 1951. (*d*) Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **65**:2067-2070 (Dec. 11) 1915. (*e*) Wren, C., and Schar, L.: Amount of Carbohydrate Required to Prevent Ketonuria in Patients After Operation, Surg., Gynec. & Obst. **90**:349-352, 1950.

2. Franks, M.; Berris, R. F.; Kaplan, N. O., and Meyers, G. B.: Metabolic Studies in Diabetic Acidosis: The Effect of Early Administration of Dextrose, Arch. Int. Med. **80**:739-762 (Dec.) 1947.

amino acids has provided some advantage [3] in that a liter of solution could comfortably provide approximately 750 calories. In order to obtain a full caloric complement, it was still found necessary in some instances to exceed the water intake of the average patient.

More recently Weinstein [4] and others [5] have demonstrated that hypertonic solutions of invert sugar could be given without significant glycosuria and without local reaction in the veins. This led to the idea of preparing a solution 1,000 cc. of which would contain 1,000 calories. It would seem that this amount approaches the physiologically normal proportion of calories to fluid in that 2,500 calories and 2,500 cc. of fluid represent very nearly the average daily requirement for the normal person. The average person eats about 45 to 50% of his daily caloric requirements in carbohydrates, 15 to 25% in protein, and 30 to 40% in fat. In accordance with these facts, we have endeavored to prepare a solution for parenteral administration which would fall within these values.

Commercial solutions of concentrated invert sugar and amino acids were used to prepare this solution. The invert sugar is an acid hydrolysate of cane sugar, each molecule of which is thereby broken down into one molecule of glucose and one

TABLE 1.—*Contents of Solution for Parenteral Nutrition*

	Total		Caloric Value, %	
	Gm.	Calories	This Solution	Ideal
Invert sugar	120	480	48	45-50
Amino acids	60	240	24	15-25
Ethanol (50 cc.)	40	280	28	30-40
Water, q. s. ad	1,000	...	..	.....
Total		1,000		

molecule of fructose. The amino acids were derived from the enzymatic digest of bovine plasma or the acid hydrolysate of casein. Absolute ethyl alcohol was added to bring up the caloric content. The solution which has proved to be most satisfactory in the average patient has the proportions given in Table 1.

One ampule of pan-vitamins [6] was added to one liter of this solution in each 24-hour period. Sodium, potassium, and other electrolytes were added to the solution as they became indicated. No incompatibilities from these additions were encountered in any instance. The amino acid preparations which were used contained

3. (*a*) Rice, C. O.; Strickler, J. H.; Orr, B., and Sanderson, D.: Parenteral Nutrition: Pre- and Postoperative Use of Glucose, Amino Acids and Alcohol, Journal Lancet **68**:91-95, 1948. (*b*) Rice, C. O.: Intravenous Therapy with Special Consideration of Parenteral Nutrition, West. J. Surg. **57**:238-242, 1949. (*c*) Rice, C. O.; Orr, B., and Enquist, I.: Parenteral Nutrition in the Surgical Patient as Provided from Glucose, Amino Acids and Alcohol, Ann. Surg. **131**:289-306, 1950. (*d*) Rice, C. O.; Orr, B.; Treloar, A. E., and Strickler, J. H.: Parenteral Nutrition in Surgery: Significance of Calories and Protein in Maintaining a Positive Nitrogen Balance, Arch. Surg. **61**:977-991 (Dec.) 1950.

4. Weinstein, J. J.: (*a*) Intravenous Infusions of Invert Sugar, M. Ann. District of Columbia **19**:179-182, 1950; (*b*) Parenteral Therapy with Invert Sugar, Ann. West. Med. & Surg. **4**:373-377 (Aug.) 1950.

5. Kerr, S. E., and Panley, R. J.: Invert Sugar as a Substitute for Glucose in Intravenous Therapy, Surg., Gynec. & Obst. **74**:925-927, 1942.

6. Eli, Lilly & Company.

variable amounts of the essential and trace electrolytes which were sufficient to provide an adequate amount in the usual uncomplicated case. Electrolyte balance studies in relation to parenteral nutrition are being pursued at present.

The excellent results which have been observed in this preliminary series of patients receiving the solution containing 1,000 calories per liter have been so unusually outstanding that it has seemed desirable to report some of our observations. The advantages of adequate parenteral nutrition need no additional emphasis at this time. They have been dealt with by many authors.[7]

METHOD OF ADMINISTRATION

The solution was given continuously through an intravenous needle in 28% of the cases, but in the remainder it was given through a polyethylene or polyvinyl tube, primarily because it was desired to give the solution slowly, around the clock. The tubing of corresponding size was threaded through a 15-gauge needle into the basilic vein near the medial epicondyle until its tip was in the large vessels of the infraclavicular region. This was done so that the infusion of fluid would be rapidly diluted with a large volume of blood. In a few instances the femoral vein was used. "Cut downs" were not employed except in rare instances.

The polyethylene tube is inserted into the vein in the operating room before the patient awakes from the anesthesia or an intradermal wheal of procaine hydrochloride is used at the site of puncture to eliminate the pain of introducing the 15-gauge needle. The tube is obturated with the use of sterile saline solution and a 1-cc. syringe, until the patient is returned to his room. It is then connected to the standard intravenous setup, and the solution is dripped slowly so that the infusion of each liter requires approximately eight hours. Since the difficulties attending the use of an intravenous needle are eliminated, there is no need to be concerned about the slow rate of administration. In fact, it is probably more economical physiologically when intravenous solutions are given slowly than when they are given rapidly.

OBSERVATIONS

The inadvertent subcutaneous infiltration of this solution has produced local redness and soreness comparable to that observed from the use of 10% glucose. This amount of local reaction is undesirable. No slough or suppuration has been observed. In an earlier series of patients in which a polyethylene tube was used exclusively, it was found that phlebitis or local redness occurred in about 18% of the cases. The local redness occurred when the tube was left in for more than three days. More recently, when the polyethylene tube has been removed at the first evidence of local reaction, the incidence of phlebitis has been less evident, as indicated in Table 2.

The type of surgical patient to whom this solution was administered is indicated in Table 2. In all patients there was a remarkable absence of undesirable systemic

7. Shafinoff, B. G. P., and Mulholland, J. H.: Effects on Human Subjects of Intravenous Fat Emulsions of High Caloric Potency, Ann. Surg. **133**:145-152, 1951. Stare, F. J., and Geyer, R. P.: Fat in Parenteral Nutrition: An Editorial, Surg., Gynec. & Obst. **92**:246-249, 1951. Wierzuchowski, M., and Laniewski, M.: Intermediärer Kohlenhydratsoffwechsel: Milchäureproduktion bei intravenöser Dauerinjektion der Glykose, Fructose und Galaktose, Biochem. Ztschr. **230**:173-186, 1931. Gardner, L. I.; Talbot, N. B.; Look, C. D.; Bernan, H., and Uribe, R. C.: The Effect of Potassium Deficiency on Carbohydrate Metabolism, J. Lab. & Clin. Med. **35**:592-602, 1950. Benditt and others.[1a] Elman.[1b] Pareira and others.[1c] Rice and others.[3] Weinstein.[4b]

reactions. Nausea and vomiting, the most commonly encountered systemic reactions associated with the administration of glucose and amino acids, were minimal when

TABLE 2.—*Data on Patients Receiving Solution*

Surgical Procedure	No. of Cases	Average No. of Days	Average No. of Liters	Polyethylene Tube Used	Intravenous Needle Used	Reaction
Gastric or colon resection	10	4.30	9.0	10	0	0
Cholecystectomy	26	3.60	6.75	22	3	Nausea (3), local redness (3), extravasation (1)
Appendectomy	27	2.58	3.58	16	11	Nausea (5), pain (1)
Pelvic surgery or laparotomy	13	3.75	5.00	10	3	Nausea (2)
Hernia	10	2.85	3.66	7	3	Nausea (1)
Miscellaneous surgery	12	3.40	6.60	12	0	Nausea (3), local redness (1)
Surgical problem (not operated on)	11	4.00	5.67	8	4	Extravasation (1)
Total	109	....	543.0	85	24	Nausea (14), local redness (4), extravasation (2)

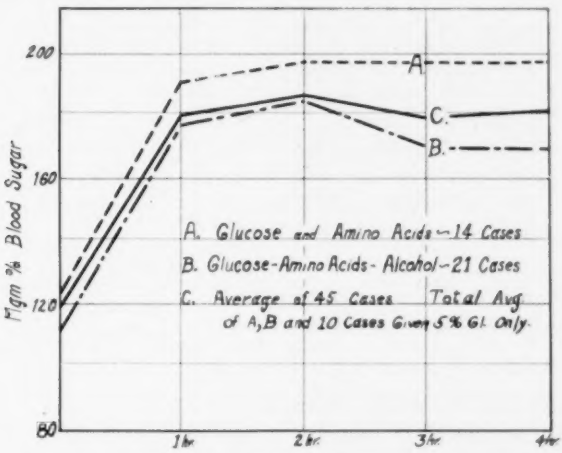


Fig. 1.—Five per cent glucose was administered intravenously over a period of four hours, providing 12.5 gm. of glucose per hour. Curve *A* represents the average blood sugar levels of 14 patients who received a liter of solution containing 5% glucose and 5% amino acids over a period of four hours. Curve *B* represents the average blood sugar levels in 21 patients who received a liter of solution containing 5% glucose, 5% amino acids and 5% alcohol at the same rate of administration. There were 10 patients who received only 5% glucose. There was no statistically significant difference between Curves *A* and *B*. The curve (not shown) which developed when glucose alone was given was not significantly different from Curves *A* and *B*. Therefore, Curve *C* was constructed from all cases. These values suggest that the simultaneous administration of amino acids and alcohol does not significantly alter the blood sugar level when glucose is given at a constant rate. It also illustrates that at this rate of administration the blood sugar level rises to approximately 180 mg. per 100 cc.

this solution was given. This result might have some relationship to a more physiologically correct proportion of carbohydrates, protein and calories, or it might be due to the slow rate of administration.

The preliminary studies which we have undertaken clearly indicate that nutrition is being maintained. Contrary to the usual experience of a weight loss of 7 to 10 lb. (3.2 to 4.5 kg.) during a 10-day period of hospital illness, there was an average gain in these patients of 2 lb. (0.9 kg.) during an average hospital stay of nine days.

That the average weight gain did not represent only a gain in water can be substantiated by an analysis of the average water balance. The water balance was determined by recording the fluid intake and fluid loss. Forty-four cubic centimeters of water for every 100 calories of the calculated metabolic requirement was allowed for insensible water loss. In the entire series the average water balance was +19 cc. per day. It seems that this could be considered to represent clinical water equilibrium.

The patients in this series received an average of approximately 15 gm. of invert sugar per hour continuously as long as the solution was used. Blood sugar levels were determined initially and during the period of infusion for 14 patients receiving the solution of 1,000 calories per liter. The levels showed an average rise from 92 mg. to approximately 160 mg. per 100 cc. These levels are below the average renal threshold and are considerably lower than those observed when glucose was given to another group of patients.

Other studies, unrelated to this series, in which 5% glucose solution was given at the rate of 1,000 cc. in four hours, providing 12.5 gm. of glucose per hour,

TABLE 3.—*Results of Nitrogen Balance Studies*

No. of Patients	Average Caloric Balance Per Day, %	Average Nitrogen Balance Per Day	Average Caloric Proportions, %			Total No. of Days	Basic Solution Represented
			Carbohydrates	Amino Acids	Alcohol		
A. 5	76	−1.15	34	24	42	37	5% glucose, 5% amino acids, 60 cc. alcohol, additional glucose and alcohol (caloric value per liter—736)
B. 4	124	+1.69	48	24	28	24	12% invert sugar, 6% amino acids, 50 cc. alcohol (caloric value per liter—1,000)
C. 8	111	+0.19	55	18	27	43	15% invert sugar, 5% amino acids, 50 cc. alcohol (caloric value per liter—1,080)
D. 2	131	+0.77	46	15	39	15	14% invert sugar, 4.5% amino acids, 50 cc. alcohol (caloric value per liter—1,160), plus additional alcohol

revealed that the average blood sugar level rose to approximately 180 mg. per 100 cc. after the first hour. The level remained at that point throughout the four-hour infusion period (Fig. 1).

Nitrogen balance studies were done on 19 patients. Different concentrations of invert sugar, amino acids, and alcohol were tried. The solution which provided 48% of the calories from carbohydrates, 24% from amino acids, and 28% from ethanol produced a positive nitrogen balance more consistently than any of the other mixtures. The average nitrogen balances are indicated in Table 3.

In Group A, with a caloric value per liter of only 736 calories, it was more difficult to obtain a positive caloric balance without overhydration. The negative nitrogen balance in this group can probably be accounted for on the basis of a low caloric balance. In Groups C and D the less favorable nitrogen balance as compared to Group B is probably due to the diminished proportion of calories from amino acids. This conclusion is based on previous studies [3d] in a group of patients suffering from malnutrition, in which it was shown that the nitrogen balance increases or decreases in relation to the proportion of amino acid calories as they pertain to the total calories (Fig. 2). The nitrogen balance figures which have been

obtained from this series of patients show an increase in relation to the more favorable caloric balance or in relation to the increase in the number of calories obtained from protein. This increase occurred even though the nitrogen balance figures did not fall into the anticipated position as would have been predicted from the graph in Figure 2. The patients in the present series were not as urgently in need of nitrogen as those from whom the graph in Figure 2 was contructed. The inset on the graph illustrates the anticipated nitrogen balance from different parenteral mixtures in a patient whose requirement is 2,500 calories and who is in urgent need of nitrogen.

The electrolyte studies done in 17 cases reveal that there was no significant disturbance during the period of parenteral feeding. The values suggest, however,

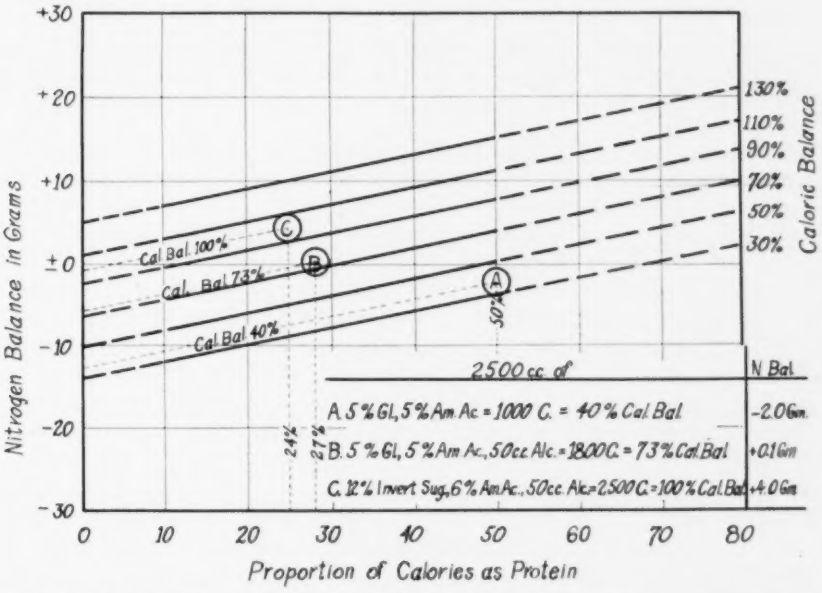


Fig. 2.—Range of nitrogen balance in relation to caloric balance. This is a composite graph reconstructed from previous studies.[3d] This graph can be used to illustrate the anticipated nitrogen balance in relation to the caloric balance in patients who are in need of nitrogen. The inset illustrates the anticipated average nitrogen balance in a patient whose caloric requirement is 2,500 calories and whose fluid requirement is 2,500 cc. daily. With the use of 2,500 cc. of 5% glucose and 5% amino acids the caloric balance would be 40%. The percentage of calories from protein would be 50%, and by projection from the corresponding abscissa and ordinate the average nitrogen balance would be expected to fall at *A*, representing approximately —2 gm. With the use of 2,500 cc. of 5% glucose, 5% amino acids and 5% alcohol, the caloric balance would be 73%. The percentage of protein calories would be 27%, and in a similar manner the average nitrogen balance would fall at *B*, representing a nitrogen balance of approximately 0 gm. With the use of 2,500 cc. of 12% invert sugar, 6% amino acids and 50 cc. of alcohol the caloric balance would be 100%, the percentage of protein calories would be 24%, and the nitrogen balance would be expected to fall at *C*, representing a nitrogen balance of approximately +4 gm.

that there may be a shift in the albumin-globulin ratio and that the potassium value of the plasma is being slightly depleted. These values are being studied more extensively in order to determine whether or not the minor changes observed in this

small series will have significance in a larger series. Average values from this group of 17 cases are indicated in Table 4.

Among the miscellaneous cases listed in Table 2, this solution was used on one occasion in a man who underwent a hemimandibulectomy and Crile neck dissection for carcinoma of the jaw. It was decided to use this method of feeding in the postoperative period rather than the more hazardous gastrostomy, which has been recommended by some authorities.

This patient gained 6 lb. (2.7 kg.) in eight postoperative days. His calculated caloric balance averaged 137%; his water balance averaged +919 cc. per day, which could account for the weight gain. The water retention in this instance was no doubt due to excessive administration of sodium chloride, as the serum sodium level was found to be 160 mEq. per liter and the serum chloride was found to be 123 mEq. per liter at the end of the parenteral feeding period.

In another instance a patient entered the hospital with a biliary fistula, having lost more than 20 lb. (9 kg.) in weight in the previous two weeks after an operation on a gangrenous gall bladder. During the first 24-hour period the amount of

TABLE 4.—*Data on Electrolyte Studies in Seventeen Cases*

	Hematocrit	Blood Urea Nitrogen, Mg./100 Cc.	Carbon Dioxide, mEq.	Chloride, mEq./L.	Blood Sugar, Mg./100 Cc.	Serum Protein, Gm.	Albumin, Gm.	Globulin, Gm.	Sodium, mEq./L.	Potassium, mEq./L.
Initial electrolyte studies	45	13.95	25.9	103.56	92.37	6.56	3.63	2.95	145.61	5.01
Third day of parenteral feeding	44	14.30	25.9	105.56	145.32	6.64	3.62	3.02	142.38	4.40
Sixth day of parenteral feeding	44	18.0	27.6	100.93	165.33	6.27	3.11	3.15	141.08	3.94

bile drainage was 1,000 cc. and his stools were acholic, but laboratory tests indicated that he did not have a complete biliary obstruction.

Within 24 hours after he had been receiving the solution containing 1,000 calories per liter, all food by mouth being eliminated, the bile drainage dropped to 60 cc. Thereafter the amount became progressively less and the biliary fistula ceased to drain. He remained on this solution for six days, receiving a caloric intake of 120% of his metabolic requirement. Nitrogen balance was positive, and the water balance was essentially in equilibrium. During this period he gained 2 lb. (0.9 kg.). Another patient with biliary fistula responded in a similar manner.

A gastric fistula developed postoperatively in a patient who underwent a partial esophagogastrectomy for carcinoma, and he was maintained on this solution for 42 days without oral feeding. During this period he had lost only 5 lb. (2.3 kg.) of his original weight. He died when an attempt was made to close the fistula.

COMMENT AND CONCLUSIONS

It has been our practice to use this solution, containing 1,000 calories per liter, almost routinely in the postoperative period until the patient is able to consume adequate food or whenever a patient is in need of fluid or calories. Parenteral nutrition with the use of the solution, in which there is a physiologically balanced proportion of carbohydrates, amino acids, and additional calories from ethanol, offers a simplification of the calculation of the nutritional intake of the patient. If the

patient receives 2,500 cc. of the solution he has received 2,500 calories, and since the numerical figures for the caloric and the fluid intake are the same, a glance at the record of parenteral fluid intake will also give the physician information concerning the number of calories received. It is our opinion that it is as important to keep a record of the caloric balance as it is to record the fluid balance.

A total of 543 liters of this solution has been administered intravenously to 109 patients without producing any permanent harmful effects. No greater local reaction in the vein was encountered than when 5% glucose was given intravenously, although we prefer to use a long intravenous polyethylene tube when continuous fluid administration is needed because of greater comfort for the patient. Extravasation of the solution into the subcutaneous tissues has produced local redness and soreness but no slough of tissue.

The continuous intravenous administration of this solution has offered a method of providing the full nutritional requirement without overhydration of the patient, as shown in these preliminary studies. The method provides a means whereby a patient can receive nutrition at the same time that he is receiving his fluid requirement.

The clinical manifestations of a smooth convalescence in patients receiving this solution have been most encouraging.

It has been our impression that electrolyte balances are more easily maintained or corrected when adequate nutrition has been provided simultaneously with this solution. Nitrogen balance studies on 19 patients demonstrated that the most favorable results occurred when the solution contained 12% invert sugar, 6% amino acids, and 5% ethanol. Water balance studies indicated that the average gain in weight was not due to water retention. There was neither polyuria nor oliguria during the period of infusion.

Blood sugar determinations during the course of the intravenous infusions indicated that the blood sugar level does not, on the average, exceed the renal threshold and it does not rise as high as has been observed when a smaller quantity of glucose was given.

The use of this method of feeding in two cases of biliary fistula suggest its advantage in diminishing the secretion of bile and allowing the irritated fistulous tract to heal. The method also offers a substitute for gastrostomy in patients who must undergo resections of the mandible for carcinoma and is also suitable for patients who must, for a short time, be nourished through a gastrostomy.

Adequate parenteral nutrition in the immediate postoperative period, which is continued until the patient is able to eat, appears to aid in the maintenance of a normal electrolyte level of the blood.

PERSISTENT OR RECURRENT PROXIMAL ILEITIS FOLLOWING SURGERY

RALPH COLP, M.D.
AND
DAVID A. DREILING, M.D.
NEW YORK

THE PERSISTENCE, progression, or recurrence of disease following surgery for nonspecific granulomatous ileitis is not as infrequent as was originally reported. It would appear that the incidence of further disease will increase in direct proportion to the length of time that the patients are followed and to the care with which they are reexamined. Table 1 lists the recurrence and mortality rates recorded by various investigators.[1] The recurrence rate for the simple exclusion

From the Surgical Service of Dr. Ralph Colp, the Mount Sinai Hospital, New York.

1. (*a*) Bockus, H. L.: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1944, pp. 16, 192-193; (*b*) Present Status of Chronic Regional or Cicatricial Enteritis, J. A. M. A. **127**:499 (Feb. 24) 1945. (*c*) Bockus, H. L.; Johnson, T. A., and Lee, W. E.: The Appraisal of the Results of Surgically Treated Chronic Regional Ileitis, Lahey Birthday Vol., pp. 53-83, 1940. (*d*) Brown, P. W., and Donald, C. J. Jr.: Prognosis of Regional Enteritis, Am. J. Digest. Dis. **9**:87 (March) 1942. (*e*) Cave, H. W.: Inflammatory Lesions of the Small Intestines: Surgical Aspects, J. A. M. A. **127**:456 (Feb. 24) 1945. (*f*) Clark, R. L., Jr., and Dixon, C. F.: Regional Enteritis, Surgery **5**:277 (Feb.) 1939. (*g*) Crohn, B. B.; Ginzburg, L., and Oppenheimer, G. D.: Regional Ileitis: Pathologic and Clinical Entity, J. A. M. A. **99**:1323 (Oct. 15) 1932; (*h*) The Prognosis in Regional Ileitis, Am. J. Digest. Dis. **3**:736 (Dec.) 1936; (*i*) Regional Ileitis, Am. J. Surg. **46**:74 (Oct.) 1939; (*j*) Regional Ileitis, Surg., Gynec. & Obst. **68**:314 (Feb.) (No. 2A) 1939. (*k*) Cutler, E. C.: Cicatrizing Enteritis, New York J. Med. **39**:328 (Feb.) 1939; (*l*) Dixon, C. F.: Regional Enteritis, Ann. Surg. **108**:857 (Nov.) 1938. (*m*) Eckel, J. H., and Ogilvie, J. B.: Regional Enteritis: Report of 21 Cases, Am. J. Surg. **53**:345 (Aug.) 1941. (*n*) Fallis, L. S.: Regional Enteritis: Case Reports, Am. J. Surg. **62**:225 (Nov.) 1943. (*o*) Felger, L., and Schenck, H. L.: Recurrence in Segmental Enteritis Following Radical Resection, Am. J. Surg. **49**:307 (Aug.) 1940. (*p*) Garlock, J. H., and Crohn, B. B.: An Appraisal of the Results of Surgery in the Treatment of Regional Ileitis, J. A. M. A. **127**:205 (Jan. 27) 1945. (*q*) Garlock, J. H.: The Present Status of the Problem of Regional Ileitis, Am. J. Surg. **72**:875 (Dec.) 1946. (*r*) Ginzburg, L., and Garlock, J. H.: Regional Ileitis, Ann. Surg. **116**:906 (Dec.) 1942. (*s*) Kiefer, E. D.: Regional Ileitis, Clinics **3**:506 (Oct.) 1944. (*t*) Kiefer, E. D., Marshall, S. F., and Brolsma, M. P.: Management of Chronic Regional Ileitis, Gastroenterology **14**:118 (Jan.) 1950. (*u*) Koster, H.; Kasman, L. P., and Sheinfeld, W.: Regional Enteritis, Arch. Surg. **32**:789 (May) 1936. (*v*) Marshall, S. F.: Regional Ileitis, New England J. Med. **222**:375 (March) 1940; (*w*) Regional Ileitis: Surgical Management and Results of Operation, S. Clin. North America **23**:873 (June) 1943. (*x*) Mixter, C. G.: Regional Ileitis, Ann. Surg. **102**:674 (May) 1935; (*y*) Regional Enteritis, Surg., Gynec. & Obst. **68**:322 (March) 1939. (*z*) Ravdin, I. S., and others: Regional Ileitis. Am. J. Med. Sc. **198**:269 (Feb.) 1939. (*a'*) Rhoads, J. E.: Management of Regional Ileitis and Certain Other Ulcerative Lesions of the Intestines, Pennsylvania M. J. **42**:1050 (June) 1939. (*b'*) Shapiro, R.: Regional Ileitis: A Summary of the Literature, Am. J. Med. Sc. **198**:269 (Aug.) 1939. (*c'*) Sneierson, H., and Ryan, J.: Regional Ileitis, Am. J. Surg. **52**:424 (Sept.) 1941. (*d'*) Warren, R., and Miller, R. H.: Regional Enteritis: Report of 43 Cases, New England J. Med. **226**:589 (April) 1942.

operation calculated from this data is 28.9%. The recurrence rate calculated for the resection operation is 21.8%. The type of surgical procedure, therefore, be it a side-tracking operation or a resection of bowel, appears to have little influence on the ultimate course of the disease. Clinical experience, rather, indicates that the fate of the patient seems to depend on whether or not the disease is definitely

TABLE 1.—*Recurrence and Mortality Rates in Regional Ileitis*

	Treatment	Year	Observer	No. of Cases	Recurrence, %	Mortality, %
1.	Ileocolostomy with exclusion	1931	Koster	15	6.7	6.7
		1937	Crohn	16	56.3	0.0
		1936	Dixon	40	50.0	2.5
		1939	Ravdin	88	28.4	7.9
		1939	Mixter	11	0.0	36.0
		1939	Rhoads	194	47.0	4.0
		1939	Shapiro	88	30.6	8.0
		1939	Crohn	20	50.0	10.5
		1940	Marshall	4	0.0	2.5
		1942	Brown	31	16.0	23.0
		1942	Warren	4	0.0	50.0
		1942	Ginzburg	54	12.0	0.0
		1945	Bockus	11	50.0	...
		1945	Garlock	57	10.5	0.0
		1946	Cave	65	13.5	0.0
		1946	Garlock	100	10.5	0.0
	Weighted average			782	28.9	4.6
2.	Ileocolostomy with resection	1935	Mixter	11	0.0	36.0
		1936	Koster	82	15.0	14.0
		1937	Crohn	32	0.0	3.1
		1938	Dixon	60	0.0	16.7
		1939	Clark	33	18.2	8.0
		1939	Mixter	278	20.0	14.0
		1939	Ravdin	290	6.2	7.2
		1939	Cutler	11	81.8	9.1
		1939	Rhoads	125	9.1	8.8
		1939	Crohn	52	7.7	15.0
		1940	Marshall	22	9.1	0.0
		1940	Felger	200	5.6	...
		1940	Bockus	0	11.1	11.1
		1941	Snelerson	22	18.4	27.0
		1941	Eckel	272	20.0	14.0
		1942	Warren	26	57.8	11.4
		1942	Brown	42	22.0	9.0
			Two stage	56	7.0	2.0
		1942	Ginzburg	23	13.0	17.4
		1943	Marshall	55	9.6	2.8
		1943	Fallis	13	30.0	6.7
		1944	Kiefer	63	19.0	...
			Mikulicz	52	0.0	2.0
		1944	Bockus	18	6.7	11.1
		1945	Bockus	35	9.6	...
		1945	Cave	55	19.5	16.3
			Two-stage	25	36.3	12.0
		1945	Garlock	45	15.4	13.3
			Two-stage	16	28.6	12.5
		1946	Garlock	100	....	13.0
		1950	Kiefer	126	34.0	...
	Weighted average			2,209	21.9	11.2
3.	Medical therapy	1942	Warren	12	8.5	16.7
		1944	Kiefer	42	48.0	7.0
	Weighted average			54	38.9	7.4
4.	Resection for recurrence	1942	Brown	23	53.0	13.0

localized and remains localized to a comparatively small area of bowel, preferably the terminal ileum.[2]

Today the surgeon treating nonspecific ileitis can expect to see at least one of every five patients return with further evidence of disease. This is a major problem and brings up for consideration two pressing questions:

1. What can be done to lower the high incidence of recurrence?
2. What should the treatment of the recurrences be?

2. Colp, R.: Proximal Extension and Progression Following Operations for Regional Ileitis, S. Clin. North America **27**:333 (April) 1947.

The purpose of this communication is to discuss these questions in general and to detail the surgical therapy applied in 10 cases with recurrent proximal ileitis.

The mechanism of persistent and recurrent disease has been clarified by the pathological studies of the various phases of nonspecific ileitis. The importance of skip areas [3] has been duly emphasized, but unfortunately these incipient areas of disease cannot always be recognized at the time of operation. They may exist as mucosal or submucosal lesions which are so small that they defy manual or visual detection. That these microscopic areas of ulceration are present and unrecognized has been proved by biopsies of material taken from presumably normal bowel used for anastomosis to the colon. In a recent case of extensive ileitis occurring in a 19-year-old girl, the intestines were excluded 45 cm. proximal to the last visible evidence of disease. A section of the ileum taken at the point of anastomosis revealed evidence, microscopically, of acute and chronic granulomatous changes. Skip areas, thus, are the usual basis for further extension or progression of the disease in the proximal ileum. The incidence of proximal recurrence, therefore, may be diminished, though probably never eliminated, by routinely defunctionalizing the ileum at a point at least 60 cm. proximal to the last gross evidence of disease, a distance which is greater than that generally advocated.

There are many instances in which the disease becomes clinically apparent many years after primary operation. In such cases it is not likely that the skip areas have remained dormant during the long symptom-free interval. It would appear more logical to postulate that the unknown etiologic agent which originally caused the disease may again have become activated. The presence of an active or dormant lesion in an excluded distal ileum probably plays no role in this type of recurrence. It is unlikely that the defunctionalized bowel acts as a focus from which the disease can travel via the mesenteric lymphatic vessels to involve the proximal bowel at or near the enterocolostomy. Postmortem examination and exploratory inspection of the excluded ileum at secondary operations indubitably support this contention. As a rule, the pathologic process in the defunctionalized bowel has undergone regression after complete diversion of the fecal current.

On the other hand, it cannot be denied that persistence of disease in an excluded ileum does occur rarely. In such cases, further ulceration from areas of disease in the side-tracked ileum may lead to fistulous communications with other intestinal loops, the sigmoid, and, retroperitoneally, the rectum. This is a serious and often lethal complication of enterocolostomy with exclusion and one of the more potent arguments in favor of the primary resection operation in all cases. Nevertheless, we do not believe that these unusual instances of persistence of disease in the excluded ileum condemn the operation of ileocolostomy with exclusion. The majority of patients do exceptionally well after the simple conservative procedure, which has a negligible mortality and morbidity. Besides, the resection of the right colon and excluded ileum may be done at a second stage, if necessary, with a lower mortality rate if a previous exclusion operation has been performed.

The problem of recurrent ileitis, then, is the treatment of disease usually in the proximal small bowel and rarely in the excluded ileum. The small group of patients

3. (*a*) Colp, R.; Garlock, J., and Ginzberg, L.: Ileocolostomy with Exclusion for Nonspecific Ileitis, Am. J. Digest. Dis. **9**:64 (Feb.) 1942. (*b*) Ginzburg, L.; Colp, R., and Sussman, M.: Ileocolostomy with Exclusion, Ann. Surg. **110**:648 (Oct.) 1939. (*c*) Colp.[2] (*d*) Garlock and Crohn.[1p] (*e*) Crohn.[11]

with the latter condition obviously require secondary resection. When the recurrence can be shown by x-ray examination to involve the small bowel diffusely, there can be little argument against medical therapy unless obstruction or perforation supervenes. Perhaps vagisection [4] will ultimately be shown to benefit these unfortunate patients. When, on the other hand, roentgenographic evidence indicates a localized recurrence in the terminal ileum, we believe that further surgical intervention is indicated. The following 10 case histories illustrate the type of procedure employed in the treatment of localized recurrent terminal ileitis, viz., division of the ileum with restoration of intestinal continuity by an ileosigmoidostomy

REPORT OF CASES

CASE 1.—H. C. was admitted to the hospital on June 9 and died on June 12, 1939. In 1928, he had undergone an appendectomy and drainage for what was thought to be acute appendicitis. A large mass consisting of cecum, appendix, terminal ileum, small intestinal mesentery, and sigmoid colon was found occupying the pelvis and the right lower quadrant. The mesentery of the terminal ileum was 2 in. (5 cm.) thick and oozed pus. The appendix was removed, and drainage was instituted. The pathologic report on the resected appendix was "acute and chronic inflammation." Eight months after the operation, the wound broke down and drained for two months. Two years later an abscess developed behind the scar. Drainage was followed by a persistent fecal fistula. At operation (1932), this fistula was found to enter a thickened, indurated, edematous, and hyperplastic terminal ileum. The affected segment was resected. The pathologic report was "hyperplastic granuloma of the terminal ileum with fistula formation." After this operation, the patient did well for five years, at which time there was a recurrence of abdominal cramps and diarrhea. X-ray examination revealed an area of diseased ileum commencing at the ileocolic stoma and extending proximally for 18 in. (46 cm.). When the abdomen was reexplored, the bowel was divided proximal to the fresh area of disease and an ileosigmoidostomy was performed, without resection of the involved segment of bowel. Postoperatively the patient was asymptomatic until two and a half years later, when he was readmitted to the hospital in a moribund condition. He died of intestinal obstruction due to a strangulating band. At autopsy, 52 cm. of excluded ileal segment was found anastomosed to the transverse colon. The proximal half of this excluded loop appeared normal; the remaining portion showed an atrophic mucosa, with longitudinal scars along the mesenteric attachment. The mesentery, itself, was slightly thickened. The site of the ileosigmoidostomy was normal, and there was no evidence of enteritis in the proximal segments.

Comment.—A primary ileocecal resection had been performed for regional ileitis. Five years later, x-ray examination revealed disease at the site of anastomosis and proximal to it. A secondary short-circuiting procedure was then performed, i. e., ileosigmoidostomy with exclusion of 45 cm. of ileum. The patient remained well for two and a half years, at which time he died of an intestinal obstruction due to adhesions. Postmortem examination disclosed no further evidence of ileitis and also a regression of the disease in the excluded loop.

CASE 2.—In 1934, S. G., a woman then 39 years of age, was operated on elsewhere for regional ileitis. A two-stage ileotransverse colostomy with ileocolic resection was performed. After this operation, she continued to suffer from attacks of pressing abdominal pain and diarrhea. She was never able to regain her normal weight. She was admitted to Mount Sinai Hospital on June 27, 1943, after recent roentgenograms showed signs of proximal extension of the ileitis.

Physical examination revealed a poorly developed, emaciated woman. Her blood pressure was 108/70. There was a well-healed right rectus scar and moderate abdominal tenderness on deep

4. Schlitt, R. S.: Response of the Distal Colon to External Stimuli in Relation to Autonomic Nerve Section for Ulcerative Colitis, Surg., Gynec. & Obst. **92**:223 (Feb.) 1951. Shapiro,[1b] Sneierson.[1c]

palpation. The hemoglobin content was 71%, the red blood cell count 3,900,000, and the white blood cell count 11,900, with a normal differential count. The urine and stools were normal.

The patient was prepared for operation with saline infusion, blood transfusions, and administration of succinylsulfathiazole (sulfasuxidine®). Prior to operation a Miller-Abbot tube was passed. Exploration was done on July 2, 1943, with the use of continuous spinal anesthesia. In the region of the ileotransverse colostomy there was some thickening, and proximal to this for an extent of about 30 cm. the ileum and mesentery showed the characteristic signs of chronic ileitis. The remainder of the small intestine appeared normal. An ileosigmoidostomy with ileal division was performed.

Postoperatively, the patient did well for about one year, at which time she lost her husband and suffered a mental breakdown. The diarrhea returned. She was admitted to another hospital on July 8, 1946, complaining of diarrhea, pain in the abdomen and high temperature for three days prior to her admission. A blood count showed a 50% hemoglobin content, 2,800,000 red blood cells, and 7,300 white blood cells, with a normal differential count. After a transfusion the hemoglobin content rose to 80% and the red blood cells to 4,500,000. Examination of the stool revealed gross blood and Salmonella typhimurium. Blood agglutination tests showed a typhoid positive reaction 1:160 and a paratyphoid positive reaction 1:160. X-ray studies failed to disclose any evidence of proximal extension of the disease. The patient received sulfasuxidine® and penicillin and was discharged improved.

She was seen on April 18, 1949. She had gained about 8 lb. (3.6 kg.) in weight and felt much better. Her bowels moved three to four times a day without cramps. Occasionally, after nervous excitement, there would be an increase in bowel movements. She was last heard from in February, 1951, at which time she was completely well.

Comment.—This patient was never well after a two-stage ileotransverse colostomy with ileocolic resection for terminal ileitis. She had probably experienced an early progression of the disease, although roentgenograms were not taken until eight years later. The roentgenograms disclosed disease in the area of the anastomosis, which at operation was shown to be chronic ileitis, 30 cm. in extent. A secondary exclusion with ileosigmoidostomy was performed. The patient was well for a year, at which time diarrhea again developed, due to a Salmonella infection. Since then she has improved, and when last seen she had no complaints.

Case 3.—C. H., a man 25 years of age, was admitted to the hospital on Oct. 30, 1943. He had undergone an appendectomy in 1941. After this procedure a fecal fistula developed, for which in November, 1942, an ileoascending colostomy was performed in an attempt to exclude the cecum. The fecal drainage persisted, however, and in April a local closure of the fistula was tried but was not successful.

Physical examination revealed a thin, well-developed man with a fecal fistula in the right lower quadrant from which a purulent discharge could be expressed. The blood pressure was 102/60, hemoglobin content 75%, leucocyte count normal and urinary findings normal. The stool was negative for occult blood.

The patient was prepared for surgery with administration of transfusions and succinylsulfathiazole (sulfasuxidine®). A Miller-Abbot tube was passed. Operation was performed on Dec. 4, 1943, through a right rectus incision with the patient under spinal anesthesia. A chronic ulcerative area of granulomatous ileitis measuring about 25 cm. in extent was found. The inflammation had spread to the cecum, and there were many inflammatory polypi, multilocular abscesses, and multiple fistulous tracts between the cecum and the ileum. The adhesions were divided, and an ileocecal resection was performed, with ileal exclusion by division about 50 cm. from the cecum. A side-to-side ileotransverse colostomy was done. The postoperative course was uneventful, and the patient was discharged on the 15th day.

He was readmitted on April 5, 1945. After the last operation, he had continued to have three soft stools daily but had gained weight. Then, after some excessive exertion, an incisional hernia appeared and the diarrhea returned. X-ray examination after a barium sulfate meal showed evidence of proximal ileal disease. The patient was readmitted because of the diarrhea and progressive weight loss. Exploration was performed on April 12, 1945, with the patient under

spinal anesthesia, through a rectus-muscle splitting incision in the left lower quadrant. There was marked induration about the stoma of the previous ileotransverse colostomy, and about 25 cm. of the proximal ileum showed evidence of the disease. The involved segments were adherent in part to the transverse colon. The ileum and its mesentery were divided through apparently normal bowel 75 cm. proximal to the previous stoma. An isoperistaltic, side-to-side ileosigmoidostomy was done. After operation the patient made an uneventful convalescence and was discharged on the eighth postoperative day.

The patient was seen on March 6, 1949. He had gained 30 lb. (13.6 kg.) in weight since his operation in 1945. His bowels moved three or four times daily except when he was under nervous strain, but there were no cramps. When last heard from, in February 1951, he was perfectly well and actively engaged in truck farming. His bowel movements were regular and formed.

Comment.—This patient, who underwent an ileocecal resection with ileotransverse colostomy for regional ileitis, suffered a proximal extension of the disease within a year. He has now remained well for over six years after an ileosigmoidostomy with ileal division.

CASE 4.—B. S., a 37-year-old woman, was admitted to the hospital on Feb. 22, 1946. She gave a two-year history of recurrent attacks of pain in the right lower quadrant, nausea, vomiting, and diarrhea. These attacks were of one to two days' duration and occurred once or twice a week. A gastrointestinal series revealed regional ileitis, and she was treated medically. During the spring and summer, while the patient was pregnant, her symptoms disappeared. The child was born in September, and in November, 1945, the attacks recurred and the pain was of increased intensity. There was occasional nausea but no diarrhea, and a loss of 12 lb. (5.4 kg.) in weight occurred within two months. Gastrointestinal roentgenograms showed a progression of the inflammation in the ileum, and surgery was advised.

The patient entered Mount Sinai Hospital thin and chronically ill. Laboratory findings showed a hemoglobin content of 66%. The erythrocyte and leucocyte counts were normal. Examinations of the urine and stool disclosed no abnormality. The serum protein level was 6.4 mg. per 100 cc. The patient was given a blood transfusion and a course of succinylsulfathiazole (sulfasuxidine®). A Miller-Abbot tube was passed. Operation was performed on Feb. 27, 1946, spinal anesthesia being used. The terminal ileum showed the signs of acute ileitis, with a markedly edematous mesentery. Proximal to this was a normal area of about 30 cm. beyond which there was another involved segment of diseased bowel measuring 12 cm. in extent. The remainder of the small intestine appeared normal. The ileum was transected about 100 cm. from the ileocecal junction, and an end-to side ileotransverse colostomy with exclusion was performed. The postoperative course was entirely uneventful, and the patient left the hospital on the eighth postoperative day.

She was readmitted on June 17, 1946, three months later, because of epigastric pain radiating to the right lower quadrant and through to the spine. This pain was associated with a 5 lb. (2.3 kg.) weight loss and diarrhea. She had been having three to four watery, mucoid stools daily. There was no blood or pus in the stools. Examination revealed a well-developed, well-nourished woman, not acutely ill. There was some tenderness in the right lower abdomen. The blood pressure was 106/70, the hemoglobin content 72%, and the white and red blood cell counts were normal. The total protein level was 5.7 gm. per 100 cc. X-ray examination with barium sulfate disclosed evidence of ileitis proximal to the stoma.

Exploration was performed on June 24, 1946, with the patient under spinal anesthesia, through a left rectus muscle-splitting incision. When the peritoneal cavity was entered, a small amount of clear straw-colored fluid escaped. The site of the previous ileotransverse colostomy was readily visualized and appeared grossly normal. Proximal to this, the ileum revealed the findings typical of ileitis. The serosa in this area was dull and thickened, and the lymph nodes were large and succulent. Approximately 90 cm. of ileum was diseased. About 150 cm. proximal to the ileotransverse colostomy, the ileum and mesentery were divided. A side-to-side isoperistaltic ileosigmoid colostomy was constructed. The patient made an uneventful recovery and was discharged on the seventh postoperative day.

She reappeared in September, 1947, complaining of frequent postprandial bowel movements and failure to gain weight. There was no abdominal pain. Recent roentgenograms had shown

no evidence of disease, but a barium enema outlined retrogradely the entire remaining jejunum, duodenum, and stomach. Operation was performed on Feb. 26, 1948. The functioning jejunum was dilated but not diseased, and the site of the ileosigmoidostomy appeared normal. The defunctionalized ileum was found to be contracted, but there was no evidence of active ileitis. It was believed that there was insufficient functioning small intestine to maintain adequate absorption. Accordingly, the ileosigmoidostomy was disconnected, and the proximal jejunum was reanastomosed to the distal, previously defunctionalized, ileum. The patient made an uneventful recovery and remained well for 18 months.

On Dec. 1, 1949, she was readmitted to Mount Sinai Hospital with a 10-day history of abdominal cramps, constipation, and weight loss. A roentgenogram of the abdomen revealed incomplete small intestinal obstruction. The patient was treated conservatively, with prompt relief of her complaints. Barium enema and barium meal examinations disclosed diffuse involvement of the functioning small intestines. It was felt that further surgical intervention had little to offer at this time. The patient accordingly was discharged.

Except for occasional attacks of transient mild nausea, vomiting, and abdominal cramps, she remained relatively well. There was no fever or diarrhea. The weight was maintained. On April 7, 1950, she returned to the hospital with vomiting, abdominal cramps, distention, and constipation. Roentgenography now disclosed no lesion in the colon or in the ileum adjacent to the functioning ileotransverse colostomy. About 8 in. (20 cm.) from this anastomosis, however, the ileum appeared rigid and narrowed and the mucosal pattern was destroyed. Despite this discouraging x-ray report and because the patient had suffered repeated attacks of incomplete intestinal obstruction, the abdomen was reexplored on April 17, 1950. At this operation evidence of disease was found in the originally excluded ileum and in the segment of functioning ileum indicated by x-ray examination, i. e., 8 in. proximal to the ileotransverse colostomy. Both areas of diseased ileum were resected, and a new jejunotransverse colostomy was constructed. This left about 4 ft. (122 cm.) of functioning small intestine.

Subsequent to this procedure, the patient was readmitted to the hospital on two occasions because of anemia, weight loss, and diarrhea. Intestinal hypermotility could be objectively proved by means of a barium meal. The transit time from mouth to anus was determined to be six hours. The oral glucose tolerance was normal, and the vitamin A tolerance was flat. The patient was vigorously treated on both occasions with transfusions, parenteral administration of vitamins, and a high protein diet. The addition of methantheline bromide (banthine), 100 mg. four times daily, to this regimen controlled the diarrhea completely. The patient was discharged (after her seventh hospitalization) on Dec. 12, 1950, gaining weight, no longer anemic, and having one to two formed stools daily. She has maintained her weight since then and has had no episodes of intestinal obstruction but continues to have diarrhea periodically.

Comment.—After an ileotransverse colostomy with exclusion for regional ileitis, the symptoms of a proximal extension developed within a short period and the abdomen was reexplored, three months after the first operation. There was extensive disease present proximal to the anastomosis, and this was excluded by an ileosigmoidostomy. After this, the patient continued to complain of diarrhea and of inability to gain weight. X-ray examination failed to reveal any signs of disease but demonstrated that the length of functioning jejunum was small and probably inadequate to maintain sufficient intestinal absorption. A third exploration confirmed the absence of active disease. The ileosigmoidostomy was disconnected, and intestinal continuity was restored by uniting the proximal jejunum to the distal, initially excluded, ileum. Within five months a fourth operation was necessary because of reactivation of the disease producing repeated attacks of intestinal obstruction. Two areas of diseased small intestine were resected, and a tertiary exclusion operation was performed, reuniting 4 ft. (122 cm.) of functioning jejunum to the transverse colon. As might have been predicted, the patient has not done well. Her complaints of weakness, anemia, weight loss, and diarrhea appear, at this time, to be the result of inadequate absorption area in the small intestine. Patients with ileitis

cannot be subjected to the massive resections of the small intestine which are being done with impunity for mesenteric thrombosis and embolism.[5] Signs of inadequate nutrition appear rapidly.

CASE 5.—F. F., a 34-year-old white woman, was admitted to Mount Sinai Hospital with the complaints of cramps, abdominal pain, and blood-tinged diarrhea. Her illness started in 1929 with the onset of severe abdominal pain. While she was under observation in another hospital in 1930, a mass developed in the right lower quadrant and the abdomen was explored. A diagnosis of sarcoma or Hodgkin's disease of the terminal ileum was made. Two courses of radiotherapy over the right lower abdomen were given, with cessation of the menses. In 1931 an abscess developed in the incision. Drainage of this was followed by a fecal fistula. Two attempts were made to close the fistula locally without success, and finally, in 1936, a portion of the ileum and cecum were resected for what was now recognized to be regional ileitis.

The patient was then symptom-free until December, 1945, when she had abdominal pain accompanied with blood-tinged diarrhea and also, for the first time, considerable mucus in the stools. Roentgenograms taken in February, 1946, showed small bowel obstruction approximately 2 cm. from the site of the ileocolostomy, with dilated loops for several feet proximal to the obstruction. Gastrointestinal roentgenograms, repeated after another course of radiotherapy, showed no significant changes in June, 1946. Because of the persistence of the symptoms and the appearance of high temperature, the patient was admitted to Mount Sinai Hospital.

Physical examination revealed a well-developed and well-nourished woman. The temperature was 101 F. and the blood pressure 98/60. There were numerous operative scars in the lower abdomen, and in the right lower quadrant there was a mass the size of a grapefruit. Peristalsis was not marked. Rectal and vaginal examinations showed no abnormalities. Laboratory investigation disclosed a hemoglobin content of 77%. The blood counts were normal. The urine was normal, and the stools contained a large number of white blood cells and red blood cells.

The patient was treated with rest in bed and a course of succinylsulfathiazole (sulfasuxidine®). Infusions of amigen® and saline were given and a transfusion of blood. After the temperature had fallen to normal, a Miller-Abbot tube was introduced into the small intestine. Operation was performed on Aug. 21, 1946, spinal anesthesia being used. Extending from the ileotransverse colostomy, the ileum for an extent of 24 cm. showed signs of subacute and chronic regional ileitis. There were many dense adhesions. The remainder of the small bowel was free of disease. The mesentery and ileum were transected at a point 50 cm. proximal to the previous anastomosis and a typical isoperistaltic, side-to-side ileosigmoidostomy was performed. The postoperative course was benign, and the patient was discharged on the ninth postoperative day.

Ten days after her discharge from the hospital, purulent drainage appeared from the previous fistula in the right lower quadrant. The mass gradually disappeared. Four weeks later abdominal cramps, vomiting, and obstipation developed. The patient was treated conservatively at another hospital for seven days, during which time the obstruction was overcome spontaneously. She was then well, with the exception of the fact that she had four to six bowel movements daily.

In November, 1946, the patient was readmitted to the hospital with abdominal cramps, vomiting, and obstipation of several days' duration. Physical examination revealed a moderately obese woman with a soft undistended abdomen. There was a draining sinus in the right lower quadrant from which pus could be expressed. Soon after admission, the patient had spontaneous relief of pain and began to have bowel movements. Gastrointestinal roentgenograms disclosed considerable dilatation of the jejunum and ileum. There was a tremendously dilated loop of small bowel on the left side of the abdomen. At 24 hours, the small bowel was empty and only a small amount of barium sulfate remained in several loops.

In view of the persistence of small bowel dilatation, it was decided to explore the abdomen despite the alleviation of acute obstructive symptoms. Operation was performed on Nov. 18, 1946, through a left lower rectus incision. The previously constructed ileosigmoidostomy stoma was normal and patent. A firm course band kinked the ileum a short distance proximal to the anastomosis. This was severed and reperitonealized. The ileotransverse colostomy stoma and

5. Cogswell, H. D.: Massive Resection of the Small Intestine, Ann. Surg. **127**:377 (Feb.) 1948.

adjoining excluded ileum, which had previously been diseased, were now completely healed. The postoperative course was uneventful.

Follow-up examination on March 15, 1948, found the patient in good health. Her bowels moved four times daily without cramps. There was still purulent drainage from the abdominal sinus. When last heard from, March 1951, the patient reported that she was in excellent health. The sinus had closed, she had gained 20 lb. (9 kg.), and her bowels moved normally.

Comment.—In this case the abdomen was first explored in 1930, at which time ileitis was mistaken for Hodgkin's disease and radiotherapy was given. Because of a fecal fistula, an ileocecal resection with ileotransverse colostomy was performed five years later. Recurrent symptoms appeared after 10 years, and exploration disclosed disease in the proximal ileum for which an ileosigmoidostomy was done. Three months later the patient was operated on for intestinal obstruction due to an adhesive band. The previously diseased ileum attached to the transverse colon was examined and was now found to be grossly normal. This demonstrates that the secondary exclusion operation induces healing in the area of recurrence in the same manner in which a primary exclusion operation results in healing of the original ileitis.

Case 6.—J. D., a 49-year-old man, became ill five years prior to his present admission to the hospital on July 10, 1947, when he began to have cramp-like, periumbilical pains, malaise, loss of weight, and nonbloody diarrhea. X-ray examination revealed the presence of gallstones. Gastrointestinal roentgenograms showed only a spastic colon. These symptoms persisted intermittently up to two years before his admission, at which time a cholecystectomy for cholelithiasis was performed. At operation the terminal ileum was found to be the seat of chronic ileitis, and an ileotransverse colostomy with exclusion was done in addition to the cholecystectomy. One year before admission, after nine months during which he was well, he again began to have intermittent diarrhea, loss of weight, abdominal cramps, and vomiting. In the past few weeks prior to his admission, he became febrile, with temperature swings up to 103 F.

Physical examination revealed a chronically ill, undernourished man. The abdomen was soft and not distended. There was a well-healed right upper quadrant scar. Rectal examination was negative. The hemoglobin content was 11.2 gm. per 100 cc., the red blood cells 3,700,000, and the white blood cells 5,300, with a normal differential count. The stools were liquid and contained traces of occult blood and a few pus cells. The urine was normal. Blood cultures were negative, as was a blood agglutination test for the typhoid-dysentery organisms. Roentgenograms of the chest were normal.

The disease ran a septic febrile course, with daily temperatures as high as 104 F. for two weeks. Administration of streptomycin in a dosage of 3 gm. each day was begun during the middle of the second week, after which the fever was lowered but did not disappear. After two and one-half weeks' of hospital care the patient was prepared for operation with transfusions, saline and amigen® infusion, oral administration of phthalylsulfathiazole (sulfathalidine®) and Miller-Abbot intubation.

On Aug. 25, 1947, operation was performed through a left rectus incision with the patient under spinal anesthesia. The ileum for a distance of 45 cm. from the previous ileotransverse colostomy presented a chronic inflammatory process. There was some plastic exudation over this portion of the bowel. The remainder of the small intestine was explored up to the ligament of Treitz and found to be normal. The previously excluded ileocecal region was not visualized, because the contents of the entire right lower quadrant were matted together by adhesions. At a point about 60 cm. proximal to the last visible area of disease, the ileum was divided and a side-to-side, isoperistaltic ileosigmoidostomy was performed.

After the operation the patient did extremely well. His temperature subsided rapidly, and bowel movements began on the fourth postoperative day. He left the hospital on the 16th day. On April 18, 1949, he entered the hospital with symptoms of incomplete obstruction of the small intestine. The diagnosis was confirmed roentgenographically, and the patient was treated conservatively, with rapid subsidence of complaints. A barium enema given after recovery disclosed no evidence of recurrent ileitis. The patient was discharged on April 26, 1949.

Since then he has continued to do well. When last heard from in March, 1951, he reported that he was gaining weight and had no cramps. There has been no further fever and no subsequent attacks of intestinal obstruction. When he is upset, he has four to six loose bowel movements daily.

Comment.—X-ray examination of this patient failed to disclose the primary regional ileitis. The disease was discovered in the course of a cholecystectomy and treated by ileotransverse colostomy with ileal division. Within nine months a proximal extension occurred, with clinical evidence of severe infection. Reexploration revealed extensive acute ileitis. After ileal division through normal bowel with ileosigmoidostomy, the acute symptoms subsided. Two years later the patient returned to the hospital with an attack of incomplete obstruction of the small intestine. A barium enema given after spontaneous recovery revealed that the region of the ileotransverse colostomy was now normal, and there were no irregularities in the adjacent ileum or in the functioning terminal ileum. The patient is well four years after the second exclusion.

CASE 7.—S. P., a 44-year-old man, had undergone a two-stage ileocecal resection for terminal ileitis at another institution six and a half years prior to his admission to the hospital on Oct. 3, 1947. The symptoms at that time were frequent watery stools and abdominal cramps. After that operation the patient felt well despite a moderate diarrhea of four to ten stools per day. Two months before his admission the patient had an episode of intestinal obstruction, for which he was treated at another hospital by means of a Miller-Abbot tube. X-ray examination showed evidence of ileitis extending at least 12 in. (30 cm.) proximal to the ileotransverse colostomy. Since then he had had cramp-like abdominal pains and diarrhea. The past history also included a duodenal ulcer.

Physical examination on admission revealed a thin, chronically ill man. There was right lower quadrant tenderness, especially over the McBurney incision, under which a matted mass could be felt. The hemoglobin content was 11.5 gm. per 100 cc., the red blood cells 3,630,000, and the white blood cells 9,900, with a normal differential count. The patient was prepared for operation with administration of sulfasuxidine® and the introduction of a Miller-Abbot tube.

Exploration was performed on Oct. 8, 1947, with the patient under spinal anesthesia, through a left rectus incision. The ileum was found to be acutely inflamed, edematous, and thickened for a distance of 65 cm. proximal to the ileotransverse colostomy. At a point 60 cm. proximal to this last involved area the ileum was divided, and a side-to-side, isoperistaltic ileosigmoidostomy was done. A biopsy of the ileum at that site showed the bowel to be normal. The postoperative course was entirely uncomplicated, and the patient left the hospital on the 10th day.

Since the second operation the patient has continued to do well. A barium meal and a barium enema given in August, 1950, revealed no abnormality of the terminal ileum, the anastomosis, or the colon. When last seen in February, 1951, the patient was gaining weight and had no complaints.

Comment.—In this case a two-stage ileocecal resection with ileotransverse colostomy was followed after six years by definite clinical and x-ray evidence of proximal recurrence. Operation disclosed an acute stage of ileitis proximal to the ileotransverse colostomy. Material was taken for a biopsy at the site of the newly constructed ileosigmoidostomy. The biopsy indicated that the anastomosis had been done through microscopically normal bowel.

CASE 8.—In 1938, S. G., a man then 24 years old, was operated on at another hospital for recurring bouts of intestinal obstruction. These attacks were of one year's duration. The operative findings were obstruction of the small intestine with generalized peritonitis. A temporary colostomy was done, and the stoma was closed several months later. For 18 months thereafter the patient was well. In 1942, however, he began to have recurrent attacks of epigastric distress, vomiting, abdominal cramps, and constipation. These attacks became more frequent and severe

until, in 1943, the patient was again hospitalized and the abdomen explored. Nonspecific terminal ileitis was found at operation and treated by ileocecal obstructive resection. After closure of the double-barrelled colostomy stoma, attacks of intestinal obstruction recurred and the abdomen was again explored. This time a simple ileotransverse colostomy was done without exclusion. The patient, however, was not relieved of his complaints. In addition, a fecal fistula appeared in the right lower abdomen. Because of the fistula and because of the persistence of complaints, a third operation was performed in 1943. No definitive procedure could be done at this time because of extensive adhesions. The patient was admitted to Mount Sinai Hospital on Jan. 12, 1944, because of the fecal fistula, almost continuous bilateral lower abdominal cramps, and recurrent attacks of vomiting with abdominal distention and constipation. There had been no weight loss or fever.

On his admission, the patient appeared well developed and well nourished. The blood pressure was 115/75. The abdomen was not distended. There was slight tenderness without spasm in the right and left lower quadrants. Three well-healed indurated scars were present in the right lower abdomen. At the lower angle of one, there was a small fistula from which pus and fecal matter could be expressed. The liver was palpable one and a half fingerbreadths below the right costal margin. There were no other abdominal masses. Rectal examination gave negative results.

Laboratory investigation disclosed a hemoglobin content of 83%, with a normal differential count. The stool contained no occult blood. Blood agglutination titers for typhoid, paratyphoid, and dysentery organisms were within normal ranges. A barium enema disclosed a normal sigmoid and transverse colon. The ileotransverse colostomy functioned well and appeared normal. In the right lower quadrant there were two loops of small intestine which were narrowed and deformed. Study of the small intestine by the injection of barium sulfate through a Miller-Abbot tube confirmed the presence of two loops of diseased ileum. These were in continuity with the fecal enterocutaneous fistula. The bowel adjacent and proximal to the ileotransverse colostomy appeared normal.

The patient was prepared for surgery with administration of sulfasuxidine.® A Miller-Abbot tube was passed. Operation was performed on Feb. 7, 1944, through a right transverse incision at the level of the umbilicus, spinal anesthesia being used. There were innumerable dense adhesions throughout the abdomen, but the distal ileum was easily identified by means of the Miller-Abbot tube. The diseased loops of ileum were matted together in the right lower quadrant and left undisturbed. The small intestine was transected in normal ileum, and an isoperistaltic, side-to-side, ileotransverse colostomy was done. There were no skip areas. The postoperative course was uncomplicated, and the patient was discharged on the 13th postoperative day.

He was last seen on Feb. 2, 1951. He has been completely asymptomatic since his operation and has gained 23 lb. (10.4 kg.). He has had two to three formed bowel movements daily.

Comment.—This case illustrates the course of severe ileitis with all the possible complications—peritonitis, intestinal obstruction, abdominal mass, and fecal fistula. During the six years from 1938 to 1944, the patient underwent seven major operations. The initial operation in the treatment of the terminal ileitis was a resection procedure, which was promptly followed by recurrence and fistula. The attempt to cure these complications with an ileotransverse colostomy in continuity was ill advised and doomed to failure. A secondary exclusion procedure, on the other hand, has been successful. The patient has remained well for seven years after this operation.

CASE 9.—J. S., a 30-year-old man, was operated on at Mount Sinai Hospital in 1936 for terminal ileitis. An ileosigmoidostomy was done as a primary procedure, followed by an ileocolic resection at a second stage. Thereafter, except for occasional loose bowel movements, the patient was asymptomatic for nine years. In 1945, he had several attacks of crampy abdominal pain and obstipation. He was hospitalized during one episode of intestinal obstruction and treated with intestinal intubation. A barium enema given during this hospital stay disclosed recurrence of disease in the ileum proximal to the ileosigmoidostomy. After this the patient was completely well for five years. In July, 1950, the attacks of generalized abdominal cramps associated with

obstipation returned. These attacks became severer and more frequent. There was no fever or diarrhea and no weight loss.

Physical examination on the patient's admission on Oct. 13, 1950, disclosed a well-developed, well-nourished young man in moderate distress due to generalized abdominal cramps. There was no fever. The heart and lungs were normal, and the blood pressure was 100/50. The abdomen was not distended, and no masses could be palpated. There was minimal generalized abdominal tenderness with spasm. No intestinal erections were visible. The bowel sounds were normal. Rectal examination gave negative results.

Laboratory investigation revealed a hemoglobin content of 12.5 gm. The leucocyte count was 9,800, with a shift to the left. A barium meal showed advanced jejunoileitis reaching as far up as the midjejunum, The diseased loops were considerably dilated, and there were complete loss of the normal mucosal pattern and marked irregularity of the intestinal contour. At the site of the anastomosis, there was partial obstruction, with distortion of the distal portion of the anastomotic loop and dilatation of the lumen. The sigmoid and the descending colon appeared normal.

Despite the x-ray findings of widespread disease, it was decided that the evidence of obstruction warranted exploration. Accordingly, the patient was prepared for surgery with the use of sulfasuxidine® and intestinal intubation with the Harris tube. On Oct. 20, 1950, exploration was performed through the previous right lower quadrant incision with the patient under spinal anesthesia. For a distance of 8 in. (20 cm.) proximal to the previous ileosigmoidostomy, the ileum appeared leathery, brawny, indurated and contracted. Proximal to this diseased area, there was 2 ft. (61 cm.) of dilated reddened bowel. The remainder of the ileum and jejunum appeared normal. The ileum was cut across proximal to both the contracted and the dilated bowel. Material was taken at this site for biopsy. An isoperistaltic, side-to-side ileosigmoidostomy was then constructed approximately 8 in. (20 cm.) above the original ileosigmoidostomy. The ileal biopsy specimen was reported as normal.

The convalescence from operation was smooth, and the patient was discharged from the hospital on the 14th postoperative day. Since then he has remained completely well.

Comment.—This case is of interest because of the long interval, nine years, following the resection operation during which the patient remained asymptomatic. In 1945 he suffered attacks of intestinal obstruction. Recurrence was demonstrated by x-ray examination. Despite this he remained well for another five years. Then, in 1950, attacks of intestinal obstruction became progressively more frequent and severer. Because of this and in spite of x-ray evidence indicative of widespread involvement of the small intestine, the abdomen was reexplored. The operative findings were at variance with the x-ray diagnosis. The disease was limited to the anastomotic loop. Therefore, it was possible to by-pass the diseased obstructed area by a secondary exclusion operation. Biopsy of the ileal segment used for reanastomosis showed normal bowel. The patient has remained well for five months following the secondary exclusion operation.

Case 10.—M. K., a 55-year-old woman, was first admitted to Mount Sinai Hospital in April, 1936. At that time she entered the hospital complaining of nausea, abdominal cramps, and diarrhea containing mucus, and, rarely, blood. A barium enema, showed an ulcerative lesion in the terminal 2 ft. (61 cm.) of ileum. The colon appeared normal. At operation on April 15, 1936, an isoperistaltic, side-to-side ileosigmoidostomy with exclusion was done for nonspecific terminal ileitis. Eighteen inches (46 cm.) of ileum was involved. After this operation the patient was absolutely free of symptoms for 12 years. Barium enemas given in 1936, 1937, and 1939 were reported as giving negative results. In 1940, a barium enema showed slight narrowing of the ileum for 4 in. (10 cm.) proximal to the ileosigmoidostomy. During the early months of 1948, the patient began to have vague abdominal cramps accompanied with nonbloody diarrhea. For the five months prior to her readmission to the hospital she had a low-grade fever and had lost 18 lb. (8.2 kg.).

At her admission to the hospital she appeared well nourished and in no acute distress. The blood pressure was 155/95. There was a soft precordial systolic murmur. The abdomen was

soft and not distended. There was no tenderness. The previous left rectus incision was well healed. In the left lower quadrant, there was a soft vague cystic mass. Rectal examination was negative.

Laboratory investigation disclosed a hemoglobin content of 11.7 gm. per 100 cc. The leucocyte count was 4,400, with a normal differential count. The stools did not contain parasites or occult blood. A sigmoidoscope could be passed for 25 cm. without encountering any areas of mucosal abnormality. A barium meal showed no abnormality in the esophagus, stomach, or duodenum. The small bowel was studied at short intervals and disclosed normal mucosal pattern and motility. The anastomosis between the ileum and the sigmoid was visualized, and no definite abnormality in this region could be demonstrated. However, a barium enema (Fig. 1) revealed a narrowing of the anastomotic loop of ileum for a short distance before and beyond the site of the ileosigmoidostomy. Proximal to the narrowed segment, the small bowel was slightly dilated. The

Fig. 1.—Barium enema showing narrowing of the lumen of the anastomotic loop and dilatation of the distal ileal limb.

large bowel filled normally to the hepatic flexure. At this point the ascending colon and cecum showed marked narrowing. The terminal ileum, visualized by reflux for approximately 2 ft. (61 cm.), showed evidence of severe ileitis.

After preparation with sulfasuxidine® and intubation of the small intestine the patient was operated on, March 22, 1948. Exploration was performed through a right rectus muscle-splitting incision with the patient under spinal anesthesia. The ileosigmoidostomy stoma was examined and found to be normal. The distal limb of the ileal anastomotic loop was dilated, as had been shown in the roentgenogram. The proximal ileum appeared grossly normal. The excluded ileum was narrowed and thickened. The cecum and the ascending colon were the seat of acute and chronic colitis. The transverse and left colon appeared normal. A resection of the right colon and the terminal ileum was performed. The pathology report on the specimen was acute and chronic ulcerative, granulomatous terminal ileitis and colitis and chronic granulomatous mesen-

teric lymphadenitis. The patient made an uneventful recovery and was discharged to a convalescent home on the 13th postoperative day.

She continued to do well. Bowel movements occurred three to four times daily and were formed. The stool contained no blood or pus but much mucus. In January, 1949, a perianal fistula developed, which was successfully cured by excision. A barium enema on March 24, 1949, disclosed a normal left colon. The ileosigmoidostomy stoma functioned well. For about 10 in. (25 cm.) proximal to the stoma the ileum was constricted, and there appeared to be a loss of mucosal pattern. Similarly, a 3-in. (7.6 cm.) segment of the distal loop appeared to be involved as well. When last seen, March 15, 1951, the patient was well and gaining weight.

Comment.—This case is unusual because of the extremely long symptom-free period following exclusion of the original ileitis. When symptoms recurred after 12 years, x-ray examination showed evidence of disease at the ileosigmoid stoma, in the terminal excluded ileum, and in the right colon. The unusual persistence of disease in excluded ileum was proved by exploration, at which time the diseased ileum and right colon were resected. The anastomotic loop and the remainder of the small intestine appeared normal despite the x-ray findings suggestive of involvement, emphasizing again the discrepancies which may be encountered between x-ray and exploratory findings.

The active pathologic process in the excluded bowel appeared in no way to have affected the ileosigmoidostomy and the ileum proximal to it. However, complete defunctionalization due to incompetence of the ileocecal valve, as revealed by roentgen studies (Fig. 1), apparently had not taken place. This perhaps explains the progression of disease from the ileum to the colon.

It was hoped that resection of the diseased ileum and colon would cure this patient. Symptomatically, this hope has been realized to date. However, there is x-ray evidence of recurrence of localized disease in the new terminal ileum. As long as the patient remains well, she will be treated conservatively in spite of the x-ray evidence of disease. It is not unlikely, nevertheless, that clinical manifestations of recurrence may appear in the future. At that time, because the disease is localized, further exclusion and a new ileosigmoidostomy can be performed.

COMMENT

Since 1934 we have advocated ileocolostomy with ileal exclusion (Fig. 2) as a primary definite procedure except in certain selected cases in which resection should be done. In a previous communication,[6] the preference for ileotransverse colostomy rather than ileosigmoidostomy was expressed. The former was purposely advised. If an extension or recurrence of the disease developed in the ileum proximal to its anastomosis to the colon (Fig. 3), the disease could again be excluded without attacking the ileotransverse colostomy by a second ileal division with ileosigmoidostomy (Fig. 4). The latter procedure is offered as a simple method of treating the problem of proximal recurrence whether the primary operation be simple exclusion or resection.

The history in the cases presented revealed that the recurrent symptoms were similar to those which characterized the initial disease. Fever of varying intensity and duration was present. In one patient (Case 6) it was septic in type. Abdominal cramps were noticed. Stools became loose in consistency and increased in number.

6. Colp, R., and Ginzburg, L.: Ileocolostomy with Exclusion in Treatment of Regional Ileitis, New York J. Med. **41**:982 (May) 1941.

Coincidentally, the signs of intermittent intestinal obstruction were occasionally observed, accompanied with abdominal distention, nausea, and vomiting. Anorexia and loss of weight and strength soon became apparent and, with these, definite anemia. Physical examination usually disclosed a distended abdomen and occasion-

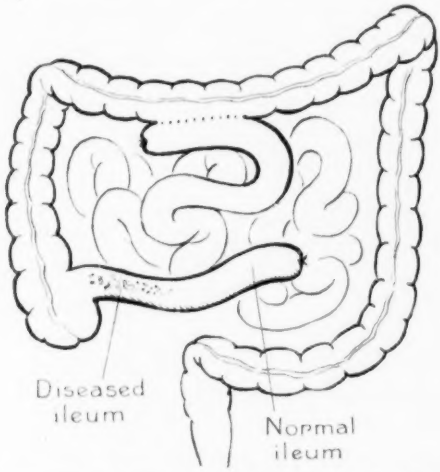


Fig. 2.—Ileotransverse colostomy with ileal division for terminal ileitis.

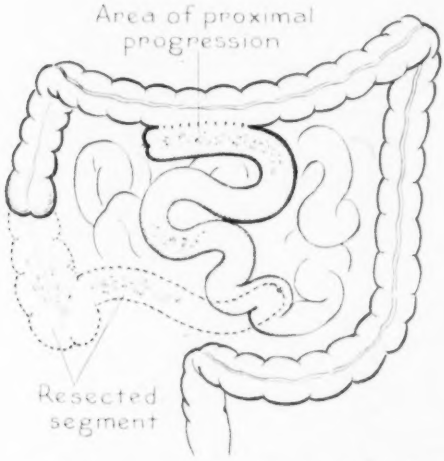


Fig. 3.—Ileocecal resection or ileotransverse colostomy with exclusion showing fresh areas of disease at the stoma and proximally at a skip area. The region marked "resected segment" corresponds to the bowel, which may also have been left excluded.

ally a tender mass in the region of the ileocolostomy. Roentgenograms after barium sulfate was given invariably pictured narrowing of the bowel proximal to the anastomosis, often so marked that a characteristic string sign was produced (Fig. 5). In some instances, the strictured areas were seen to alternate with bowel of

normal caliber, and occasionally a partial stenosis of the ileocolic stoma was visualized. Surgery was advised in these cases because the recurrent disease appeared to be progressive and nothing seemed to be accomplished by conservative medical supportive therapy.

Before operation the patients were given a high protein diet and the necessary vitamins, especially B complex, reinforced by dextrose, saline, whole blood, plasma, and protein hydrolysate given parenterally. Sulfasuxidine® or sulfathalidine® were prescribed orally. The Miller-Abbot tube was passed routinely and proved to be of inestimable value. Not only does it decompress the small bowel, if partially obstructed, but also, at the time of operation, the tip of the tube points in the direction of the distal ileum. If the tube were not introduced, the identity of the ileal loops could only be established by tracing the intestine down from the ligament of Treitz. This is often a difficult as well as a shocking procedure, especially when one is dealing with a mass of matted inflamed bowel intimately attached to the

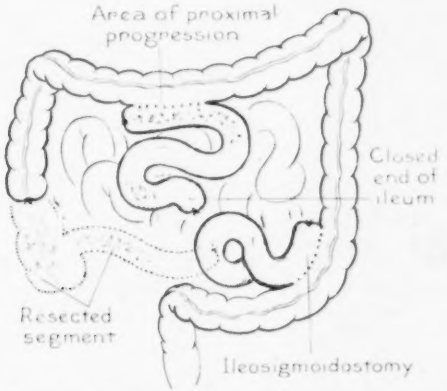


Fig. 4.—Secondary ileal division with ileosigmoidostomy for proximal recurrence of ileitis previously treated with ileotransverse colostomy with or without resection.

surrounding viscera. Postoperatively the Miller-Abbot tube maintains intestinal decompression.

Spinal anesthesia was used routinely. The abdomen was usually opened through a lower left rectus muscle-splitting incision. When the peritoneal cavity was entered, the entire small bowel, usually shirred on the Miller-Abbot tube, was carefully examined for evidences of skip areas. The extent and character of the local pathologic changes were then noted. Invariably, acute and chronic ileitis starting at or near the site of the previous ileotransverse colostomy and extending proximally for a variable extent with skip areas was found (Fig. 3). Fortunately, in none of the patients of this series was a diffuse, inoperable jejunoileitis present.

The surgery performed in all 10 cases was conservative. The area of recurrent ileitis was not resected. It was simply excluded, the diseased segment of bowel remaining attached to the transverse colon. A second ileal division was performed approximately 60 cm. proximal to the last visible evidence of disease and an ileosigmoidostomy was constructed (Fig. 4). Sufficient small intestine must be left to insure adequate nutrition. This apparently was not done in Case 4. Eventually

intestinal continuity had to be restored by a side-to-side jejunoileostomy in order to secure adequate bowel for intestinal absorption.

The fear that implantation of the proximal ileum into the sigmoid might lead to a serious and persistent diarrhea has never been substantiated. In fact, previous studies [3b] have noted no difference in bowel function after either ileotransverse colostomy or ileosigmoidostomy. It has been demonstrated that the contents of the small bowel, if adequate in extent, on entering the colon pass retrogradely for a distance evidently sufficient to allow the water-absorptive phenomenon to occur. This results in a semisolid stool. In a few cases, there has been a persistence of frequent bowel movements, worse during periods of stress and strain. The possibility that the blind ascending and proximal parts of the transverse colon may become distended and filled with scybala has never been observed.

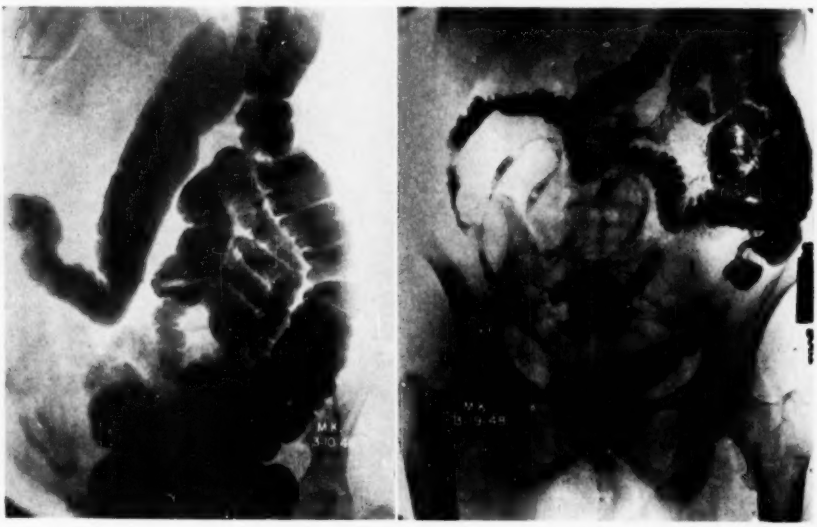


Fig. 5.—Barium enema illustrating classical "string sign" and dilated loop of small intestine in a case of regional ileitis. The patient had undergone an ileosigmoidostomy with exclusion for ileitis. The proximal ileum is normal. The excluded ileum has been filled retrogradely. The cecum and ascending colon also appear to be diseased (Case 10).

In cases in which there is recurrence after either resection or exclusion and in which an ileotransverse colostomy has been performed, ileal division with ileosigmoidostomy offers a conservative solution to a complicated problem in which radical surgery may be extremely hazardous. It may be technically difficult to take down a previous anastomosis and separate edematous friable bowel from other viscera. Resection of this type of intestine with its thickened edematous gland-bearing mesentery often produces shock in the patient.

The postoperative follow-up on these patients has shown fairly satisfactory results. Some of them, particularly during periods of emotional upset, have had frequent bowel movements, but not to a distressing degree. No symptoms have developed thus far which could be attributed to the presence of the isolated ileal loop which was left attached to the transverse colon. There is ample evidence that

the disease in the defunctionalized bowel regresses to much the same extent as it does in the primarily excluded ileum. In one patient (Case 1) who succumbed two and one-half years after secondary ileosigmoidostomy with ileal division for recurrent ileitis following a primary ileocolic resection with ileotransverse colostomy, autopsy revealed that the excluded bowel, which measured 27 cm. in length from the point of its anastomosis to the transverse colon, was grossly normal and that there was no further evidence of disease. In another patient (Case 5) who entered the hospital for an intestinal obstruction three months after a secondary ileosigmoidostomy

TABLE 2.—*Ten Cases of Proximal Recurrent Ileitis Treated by Secondary Ileal Division*

Case and Sex	Primary Operation	Interval Between First and Second Operation, Yr.	Secondary Operation	Period of Follow-Up After Second Operation, Yr.	Present Status
1 Male	Ileocecal resection, ileotransverse colostomy	5	Ileal division with ileosigmoidostomy	2½	Died*
2 Female	Ileocecal resection two-stage, with ileotransverse colostomy	5	Ileal division with ileosigmoidostomy	8	Well
3 Male	Ileocecal resection, ileotransverse colostomy	1½	Ileal division with ileosigmoidostomy	6	Well
4 Female	Ileotransverse colostomy with exclusion	½	Ileal division with ileosigmoidostomy	5	Secondary recurrence†
5 Female	Ileocecal resection, ileotransverse colostomy	9	Ileal division with ileosigmoidostomy	5	Well
6 Male	Ileotransverse colostomy with exclusion	2	Ileal division with ileosigmoidostomy	4	Well
7 Male	Ileocecal resection, two-stage, with ileotransverse colostomy	6	Ileal division with ileosigmoidostomy	3½	Well
8 Male	Ileocecal obstructive resection	1	Ileal division with ileotransverse colostomy	7	Well
9 Male	Ileocecal resection, two-stage, with ileosigmoidostomy	14	Ileal division with ileosigmoidostomy	5	Well
10 Female	Ileosigmoidostomy with exclusion	12	Ileocolic resection	3	Well;‡ proximal recurrence

* Patient died of an acute intestinal obstruction. No evidence of recurrent disease.
† Abdomen was explored after 18 months because of diarrhea and weight loss. The excluded ileum was found to be healed and restored to intestinal activity. Abdomen was reexplored five months later for intestinal obstruction. A tertiary ileotransverse colostomy excluding the secondary recurrence was performed.
‡ The patient is clinically well, but x-ray evidence of proximal recurrent ileitis is present.

with ileal division for proximal recurrence, exploration disclosed that the acutely inflamed bowel which had been previously excluded was now entirely normal in appearance. In Case 6, in which an acute proximal recurrence was excluded, a barium enema given two months after operation showed that the local inflammation in the region of the ileotransverse colostomy had subsided.

The length of the symptom-free interval following the primary operation for ileitis can be surprisingly long. This is illustrated by three cases (Cases 5, 9, and 10), in which the interval was 10, 14 and 12 years. Freedom from complaint does not necessarily mean eradication of disease. In Case 9, after nine years of complete well-being, recurrence was demonstrated by x-ray examination. However, the patient remained well for five more years despite the recurrence. In Case 10 per-

sistent disease in an excluded loop was eradicated by resection after 12 symptom-free years. This procedure was followed by an asymptomatic proximal recurrence which has lasted, to date, two years.

The incidence of intestinal obstruction in these patients is appallingly high. In six cases (Cases 1, 4, 5, 6, 8, and 9) of the 10 there were episodes of intestinal obstruction. This was due to intrinsic bowel disease in four instances (Cases 4, 6, 8, and 9) and to adhesive bands in two (Cases 1 and 5). Only one patient (Case 6) escaped reoperation for the intestinal obstruction. One patient (Case 1) died after release of an obstructing adhesive band.

Case 8 deserves special mention. The patient had all the complications of regional ileitis, viz., peritonitis, intestinal obstruction, abdominal mass, and fecal fistula. In six years he underwent seven major operations for his disease. A complete cure (seven years' follow-up) was obtained by a secondary ileal division with ileotransverse colostomy.

The results of the secondary exclusion operations are summarized in Table 2. Among the 10 cases there was one death (Case 1), due to intestinal obstruction occurring in a clinically cured patient two and one-half years after the secondary exclusion operation. Of the nine patients who were treated by the procedure, there has been a tertiary recurrence of the disease in only one (Case 4). The recurrence rate for the secondary exclusion operation in this series is 11.1%. Seven patients are well and restored to active life.

SUMMARY

Recurrent symptoms following either resection or exclusion for terminal ileitis are not as rare as originally reported. The recurrence rate calculated from reports in the literature is above 20%. The symptoms are due to a progression of the disease in the proximal ileum at or near the point of anastomosis to the transverse colon. Rarely are the complaints due to a persistence of disease in the excluded ileum. The usual recurrence results from skip areas of incipient disease in the proximal ileum which are present at the time of anastomosis to the transverse colon. The symptoms, physical signs, and x-ray findings in this type of recurrent ileitis are similar to those of the primary disease. In cases in which an ileotransverse colostomy has been previously performed, the treatment of choice is a secondary ileal division with ileosigmoidostomy. The point of ileal division should be at least 60 cm. proximal to the last visible segment of disease. It is advisable at the time of operation to make a biopsy of the ileum at the site at which the new anastomosis is to be made.

The follow-up results in 10 cases of recurrent proximal ileitis treated with a secondary exclusion operation are presented and discussed. The secondary recurrence rate for this procedure was 11.1%.

CORTICOTROPIN (ACTH) IN TREATMENT OF KELOIDS

HERBERT CONWAY, M.D.
AND
RICHARD B. STARK, M.D.
NEW YORK

THE WELL-DOCUMENTED reports of the effect of corticotropin (ACTH) in reducing fibroplasia stimulated our study of this agent in the treatment of keloids.[1] Two methods were used: First, the keloids were excised and the patient was treated with corticotropin in the postoperative period. Second, corticotropin was combined with hyaluronidase and injected directly into the keloid.

I. SURGERY AND POSTOPERATIVE ADMINISTRATION OF CORTICOTROPIN

The first patient was a child 2 years old who had a large confluent keloid which fused the first, second, and third toes of the right foot into one mass of reddened, elevated scar. This keloid, which developed after surgical treatment for syndactylism at another hospital, completely obliterated the interdigital spaces. That this lesion was a true keloid rather than a hypertrophic scar was evidenced by its growth into cutaneous areas beyond the site of original surgical trauma. Keloidal tissue was excised *in toto*; the raw surfaces were covered with split-thickness skin grafts. After this, 60 mg. of corticotropin were given daily for two days. This was reduced to 40 mg. for the next 20 postoperative days. This patient has been followed for eight months. Although scar has formed at the junction of the graft with normal skin, there has been no evidence of the expected luxuriant regrowth of keloid.

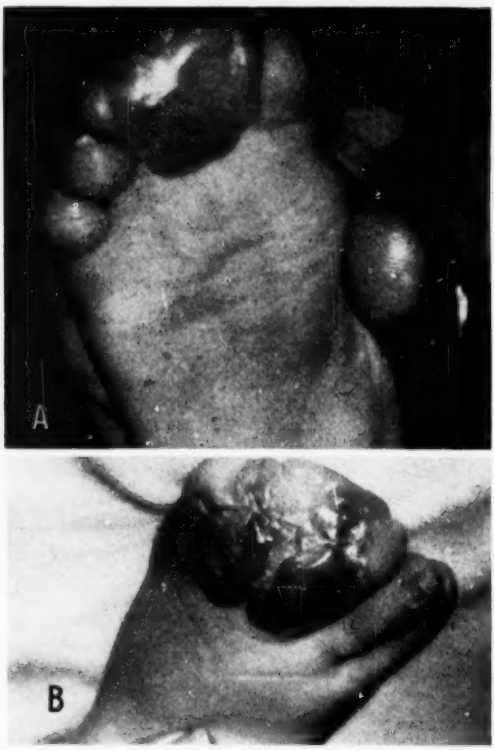
This work was aided by United States Public Health Service Grant No. H-466.

From the Department of Surgery (Plastic) of the New York Hospital and Cornell University Medical College.

1. Spain, D. M.; Molomut, N., and Haber, A.: Biological Studies on Cortisone in Mice, Science **112**:337, 1950. Ragan, C.; Howes, E. L.; Plotz, C. M.; Meyer, K.; Blunt, J. W., and Lattes, R.: The Effect of ACTH and Cortisone on Connective Tissue, Bull. New York Acad. Med. **26**:251, 1950. Conference on Connective Tissues: Transactions of First of Conference, New York, April 24-25, 1950, edited by C. Ragan, New York, Josiah Macy, Jr., Foundation, 1951. Howes, E. L.; Plotz, C. M.; Blunt, J. W., and Ragan, C.: Retardation of Wound Healing by Cortisone, Surgery **28**:177, 1950. Cornman, I.: Selective Damage to Fibroblasts by Desoxycorticosterone in Cultures of Mixed Tissues, Science **113**:37, 1951. Baker, B. L., and Costor, C. W.: Cutaneous Atrophy Induced by Local Treatment with Adrenocortical Steroids, Anat. Rec. **106**:173, 1950. Creditor, M. C.; Bevans, M.; Mundy, W. L., and Ragan, C.: Effect of ACTH on Wound Healing in Humans, Proc. Soc. Exper. Biol. & Med. **74**:245, 1950. Baxter, H.; Schiller, C.; Whiteside, J., and Straith, R. E.: The Influence of Cortisone on Skin and Wound Healing in Experimental Animals, Plast. & Reconstruct. Surg. **7**:24, 1951. Plotz, C. M.; Howes, E. L.; Meyer, K.; Blunt, J. W.; Lattes, R., and Ragan, C.: The Effect of the Hyperadrenal State on Connective Tissue, Am. J. Path. **26**:709, 1950. Stinchfield, F. E.: Experimental and Clinical Use of Oxidized Cellulose and Cortisone in the Prevention of Excess Bone and Fibrous-Tissue Formation, J. Bone & Joint Surg. **32-A**:739, 1950.

The second patient exhibited a keloid over the deltoid region which measured 5 by 3 cm. This was excised completely. Closure of the wound was effected with a subcuticular pull-out wire, no sutures or ligatures having been buried. One hundred milligrams of corticotropin were given for the first 10 postoperative days. This patient has been followed for five months, with no evidence of hypertrophic scarring or keloid formation.

A third patient with a keloid similar to that of the second patient was operated on, with the use of this same surgical technique. For control purposes, no cortico-



A and *B*, large confluent keloid obliterating interdigital spaces in a child who had been operated on for syndactylism.

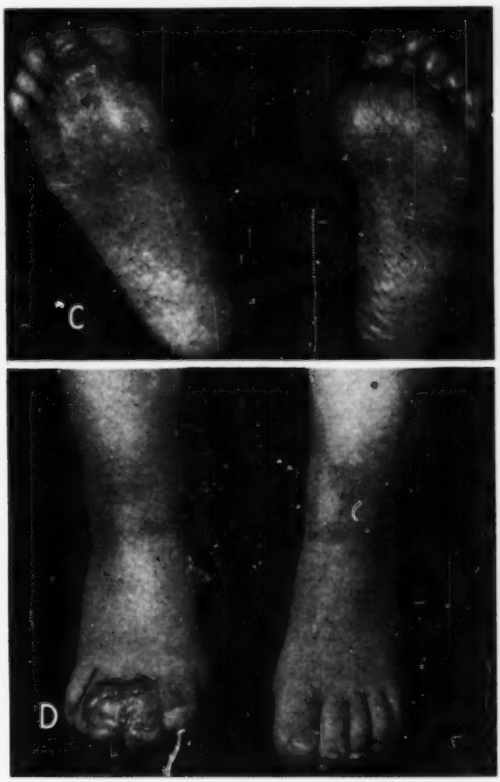
tropin was administered in the postoperative period. The keloid was in the intermammary region. Three weeks after operation, the scar again became hypertrophic and markedly symptomatic, the patient complaining of pain and itching.

II. INJECTION OF CORTICOTROPIN AND HYALURONIDASE INTO KELOIDS

A second series of four patients were treated by intrakeloidal injections of corticotropin. This was mixed with hyaluronidase [2] to disseminate widely the active

2. Wydase, lyophilized hyaluronidase, supplied by Wyeth, Inc., Philadelphia.

agent (corticotropin) which itself exerts an antipermeability effect. The enzyme, hyaluronidase, exerts its action on the substrate, hyaluronic acid, a mucopolysaccharide present normally in the ground substance of skin,[3] connective tissue, synovial fluid, aqueous humor, umbilical cord, and other tissues. Its action combats that of hyaluronic acid, which "binds water in the interstitial spaces . . . holds cells together in a jelly-like matrix and serves as a lubricant and shock-absorber in joints."[4] There is experimental evidence that cortisone and corticotropin will reduce



C and *D*, eight months after keloid excised and toes grafted while patient was being given corticotropin therapy. There is no recurrence of the keloid. The toes were isolated by thick-split grafts of skin. Corticotropin was given for 22 days after operation.

somewhat the spreading of hyaluronidase, as will heparin, parathyroid, posterior pituitary, animal sera, and chondroitin sulfate.[5] However, diluted with large

3. Hudack, S. S.; Blunt, J. W.; Higbee, P., and Kearin, G. M.: A Probable Acid Mucopolysaccharide Present in Granulation Tissue, Proc. Soc. Exper. Biol. & Med. **72**:526, 1949.

4. Meyer, K.: Biological Significance of Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**:335, 1947.

(Footnotes continued on next page)

amounts of hyaluronidase, the corticotropin was observed to spread as rapidly in the dense keloid as does hyaluronidase alone.

The rationale of mixing corticotropin with hyaluronidase is to achieve a widespread dissemination of corticotropin in the keloid. A sufficient amount of hyaluronidase was used so that an injection of 1 cc. could be instilled comfortably into the keloid within a matter of about three minutes. The first patient had a good response in the amelioration of the symptoms and signs of her keloid. Her itching and pain disappeared completely within the first course of five injections given at weekly intervals, and the keloid softened and blanched. Pain in the left arm, which radiated from the keloid over the deltoid region, prevented raising that arm to comb her hair. The pain disappeared entirely after several injections. This patient was the only one of four in whom the physical properties of the keloid were affected. In all four, however, the symptoms abated or completely ceased. The patient was kept on a regimen of 12.5 to 25 mg. of corticotropin weekly (125 to 250 turbidity-reducing units of hyaluronidase), and after her first course of therapy was complete she was given a respite for one month. Then an additional, similar course of therapy was given. The second course accomplished little except to soften the keloid still further and to effect slight additional blanching. There was, however, no itching or pain at any time after the first course of therapy. The patient has been free from symptoms for three months.

The second patient had two keloids over the left deltoid region as a result of vaccination. These keloids were of similar size and shape, measuring 2 by 2.5 cm. The posterior keloid itched markedly and the anterior slightly, and both were painful. The posterior keloid was treated for five weeks with corticotropin and hyaluronidase. After the first treatment, there was no further itching or pain, and the keloid became slightly softer and less erythematous. After five weekly injections, therapy was discontinued for one month. A second course of therapy was given for the anterior keloid consisting of intrakeloidal injections with hyaluronidase alone. This keloid showed no change in physical signs. The slight itching had ceased after the first course of therapy. Two other patients were treated, each being given one course of five weekly injections of corticotropin and hyaluronidase. In these cases also the physical signs of the keloid were unchanged but all itching and pain ceased. These symptoms usually disappeared after the first or second treatment.

From our experience with this limited series of cases, it appears that symptomatic relief can be afforded patients with keloids by the intrakeloidal injection of corticotropin to which a spreading factor (hyaluronidase) has been added. It is felt that this therapy may be superior to x-ray therapy for alleviation of symptoms of a keloid. The treatment offers litle for the appearance of the keloid itself. A single injection may be sufficient to relieve itching and pain. The question of whether it is necessary to inject directly into the keloid or to inject parenterally at any site remains for clarification by future clinical research.

5. Seifter, J.; Baeder, D. H., and Dervines, A.: Alteration in Permeability of Some Membranes by Hyaluronidase and Inhibition of this Effect by Steroids, Proc. Soc. Exper. Biol. & Med. **72**:136, 1949. Weinstein, L.: Further Studies on the Prophylaxis of Experimental Infections and Intoxications with Various Hormone Preparations, Yale J. Biol. & Med. **12**:549, 1940.

SIMPLE PERCUTANEOUS TECHNIQUE OF STABLE NAILING OF FRACTURES OF THE NECK OF THE FEMUR

HEINZ GELBKE, M.D.
GOETTINGEN, GERMANY

THE VALUE of nailing fractures of the neck of the femur is beyond doubt, but a high percentage of unsatisfactory late results (pseudarthrosis, necrosis of the head of the femur, redislocations) shows that all problems pertaining to nailing are not entirely solved. Much attention should be paid to its mechanical and technical aspects.

The following points should be noted by the surgeon in nailing fractures of the femoral neck:

1. The osteosynthesis must be stable, because immobility in the fractural space is absolutely essential for osseous healing.

2. The technique should be as simple as possible so that each surgeon is able to work with a minimum amount of instruments and other complicated apparatus.

3. The incision should be as small as possible and the operative trauma minimal, as fractures of the neck of the femur usually happen in elderly persons. This point of view is very important, especially in cases of certain intertrochanteric fractures in which a large incision is necessary when nailing is done with an angled nail, according to Jewett.

In regard to point 1, the more horizontal position of the nail following the axis of the neck is not stable as the nail lies entirely in spongy bone. There is thus the possibility of the tip being pushed down and the end being pushed up by the mechanical forces acting at the head of the femur and thereby displacing the caput downward (Fig. 1*A*). This brings about pseudarthrosis and redislocations. On the other hand, when the nail is placed more at an angle of inclination (forming an acute angle with the midline of the body as shown in Figure 1*B*), the end of it is firmly anchored in the cortical layer of the femoral shaft and the middle third rests tangentially on the lower arch of the neck (Adam's bow). In this way the tip of the nail cannot sink downward. The optimal mechanical conditions are fulfilled, and the position of the nail is the resultant of the parallelogram of forces. This method has been well stressed by Kuentscher.[1]

In regard to point 2, this more vertical or slanting position of the nail has another advantage in that the right position can be found automatically without any complicated target instrument (Fig. 4). As the position of Adam's bow where

From the Surgical University Clinic, Goettingen, Germany. (Director, Professor Hans Heller, M.D.)

1. Kuentscher: Die Marknagelung, Berlin, Verlag Dr. Werner Saenger, 1950.

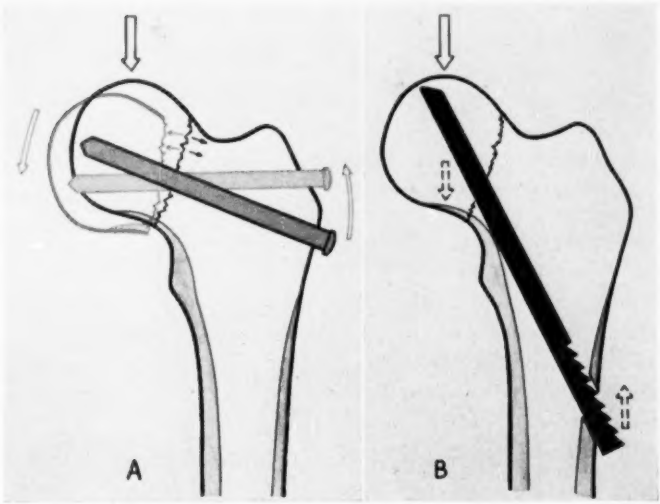


Fig. 1.—*A* shows the tendency for the nail and the head of the femur to be displaced when the nail occupies a more horizontal position, which results in instability and may cause pseudarthrosis or redislocation. *B* shows the stable mechanical conditions which exist when the nail is more slanting or inclined. It is evident that this position of the serrated V-shaped nail, with its end anchored in the cortical layer of the shaft, is also suitable for a high number of intertrochanteric fractures.

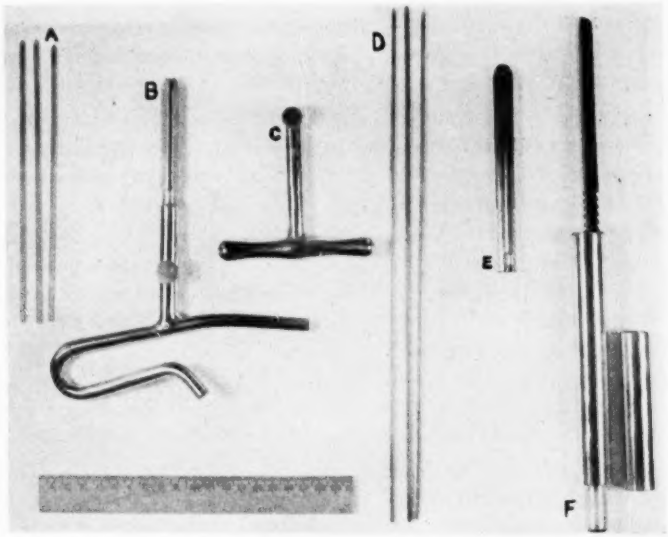


Fig. 2.—Special instruments needed for percutaneous stable nailing. *A*, three marking nails; *B*, trochar drill; *C*, handle of the guiding pike; *D*, three guiding pikes; *E*, V-shaped nail with serrations; *F*, instrument for holding and driving in nail.

the nail slips over is constant, one has only to determine the point of entry of the nail. These two points (Adam's bow and the place of entry of the nail on the shaft of the femur) give the definite position of the nail.

In regard to point 3, the point of entry can be percutaneously located by marking nails and roentgen controls (Fig. 3). When the point of nail entry has been located, one can drill a passage for the nail by making only a buttonhole incision in the soft tissues, and a minimum amount of operative traumatism is incurred.

INSTRUMENTS

The instruments used for this operation are simple and few in number. They are as follows (Fig. 2): *A*, a few marking nails, 17 cm. long, without a head. *B*, a trochar-like drill, 16 cm. long, with the external diameter 13 mm. and the internal lumen in accordance with the size of the marking nails. The trochar drill is provided with a screw in order to fix the marking nail within the drill. This drill is complete with a handle. The lower band of the handle is twisted to one side in order to give room for insertion of the long guiding pike. *C*, a handle for the guiding pike. *D*, guiding pikes, 33 cm. long and of the same caliber as the marking nails. *E*, V-shaped nails varying from 13 to 15 cm. in length and of such a size (13 mm.) that they can conveniently pass through the drill hole in the bone. Their shape is similar to the shape of the Kuentscher nails, and they are known in Germany as Becker nails. They have been modified by means of saw-like serrations at the end in order to prevent their being pushed backward when placed in a slanting position. The end of the nail is provided with an oval opening enabling the surgeon to draw it out. The advantages of this V-shaped serrated nail are manifold: It can be constructed at a low cost. There are no mechanical disadvantages, i. e., the guiding pike does not get cramped in or closely pressed during the manipulation. This type of nail is sufficient to prevent rotation of both sides of the fracture. *F*, a holding and driving-in instrument for the V-shaped serrated nail. This instrument has a V-shaped groove to hold the nail and a lumen for the passage of the guiding pike. It has also an adjustable lengthening part, a metal graduated ruler and the usual surgical instruments, including one for drawing out Kuentscher nails.

OPERATIVE TECHNIQUE

The operative method is demonstrated in Figures 3, 4, and 5 and should be as follows: After reposition of the fracture, one of the marking nails is introduced percutaneously into the lateral cortical layer below the greater trochanter. A roentgenogram will now show in which position the V-shaped nail would lie, taking the point of this marking nail as entry (Fig. 3). If the first marking nail does not show the proper entry for the V-shaped nail, a second or perhaps third marking nail is needed to give the proper entry for the V-shaped nail (Fig. 3). Once the exact point of entry is ascertained by means of an anteroposterior roentgenogram, an important point of this technique is to see that the marking nail is situated more dorsally. This can be done only by knocking on the bone with the tip of the marking nail to get an idea of the girth of the shaft of the femur. On no account should the marking nail (and thereby the entry of the V-shaped nail) be placed more on the ventral half of the girth of the femur.

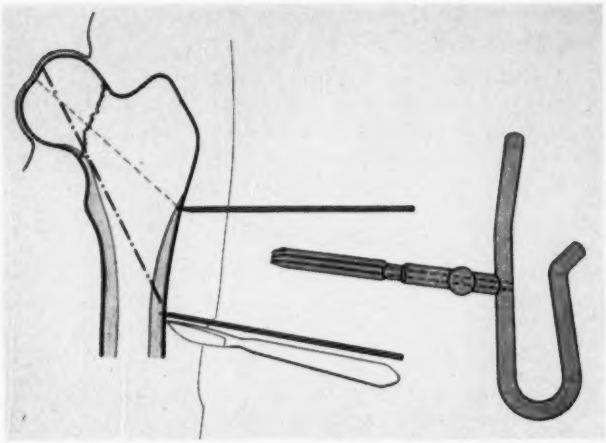


Fig. 3.—Ascertaining the entry of the nail by means of percutaneous marking nails.

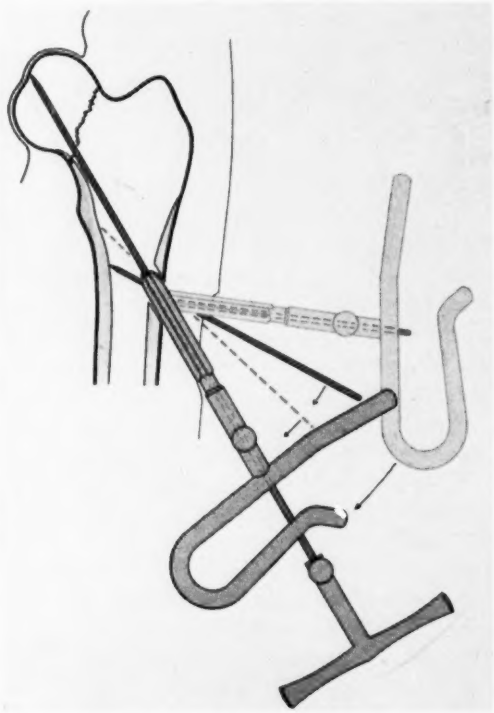


Fig. 4.—Drilling the passage for the entry and ascertaining the exact position of the nail by means of the guiding pike slipping over Adam's bow of the femoral neck.

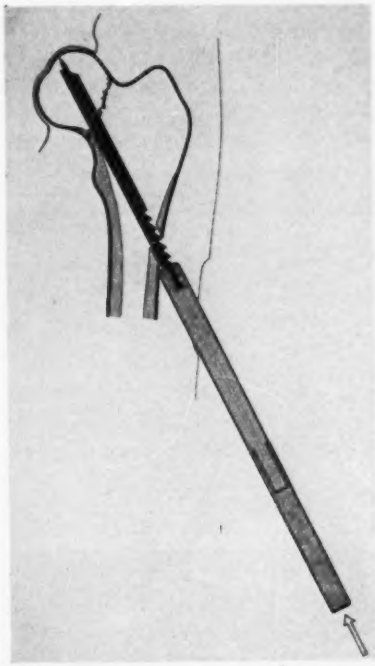


Fig. 5.—Driving in and final position of the nail.

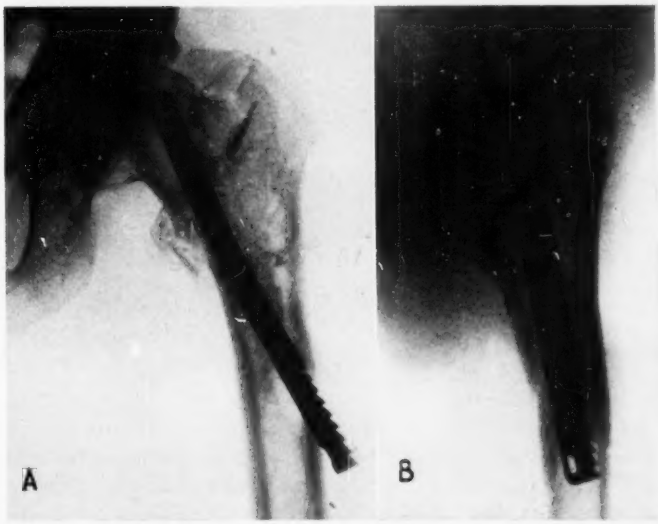


Fig. 6.—*A* and *B* show an intertrochanteric fracture nailed percutaneously. Six weeks after operation a stable mechanical condition exists.

A small incision on to the bone is now made along the properly placed marking nail after the other marking nails have been removed. The trochar drill is allowed to glide over this marking nail till it comes in contact with the bone. The screw on the drill is tightened. The drill is probed in with a turning movement sideways (right and left, but not taking a full turn movement as in screwing) with full

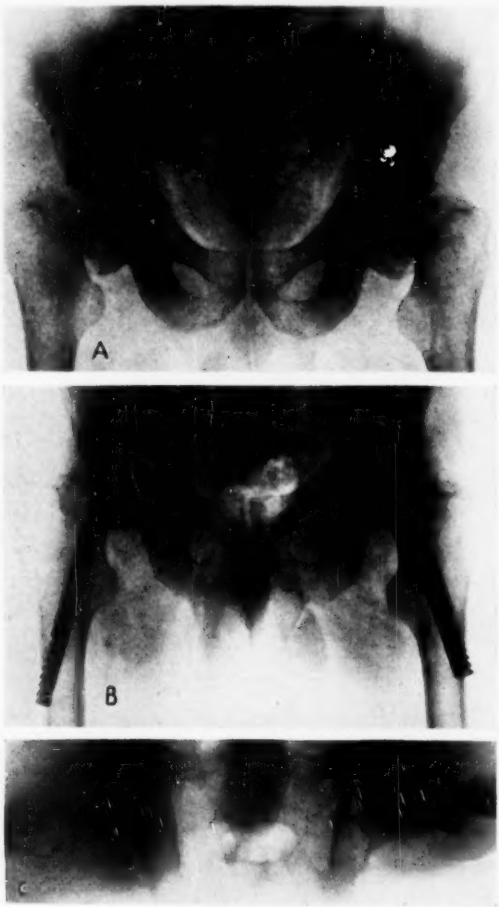


Fig. 7.—*A* shows a bilateral intracapsular fracture of the neck of the femur. *B* and *C* show the condition six months after nailing, with proper bony healing.

pressure and contact on the bone. When half of the cortical layer is pierced, the handle of the drill is moved distally without tilting it upward or downward. By this means the canal that is made by drilling takes a proximal and medial direction toward the head of the femur. When the cortical layer is pierced, the entry of the drill into the marrow cavity is easily felt. The marking nail is now removed, and the guiding pike is introduced.

The guiding pike is gradually pushed in till it knocks against the cortical layer of the opposite side. By a forward and backward movement, knocking on the medial cortical layer and making an acute angle with the midline of the body, the guiding pike suddenly slips over Adam's bow and is pushed into the head of the femur (Fig. 4). If the guiding pike is not tilted while it is being pushed in, it occupies an accurate position in the first attempt. At this stage the drill is removed and the guiding pike is allowed to remain if a roentgenogram taken from both sides shows the pike to be in the proper position.

The length of the V-shaped nail is easily determined by taking the length of the portion of the guiding pike that is out of the bone and subtracting it from the entire length of the pike (33 cm.). The usual length of the V-shaped serrated nails ranges from 13 to 15 cm. The V-shaped nail is pushed in with the instrument for holding and driving in, which has already been described. The final depth of the nail is again roentgenologically determined (Fig. 5). The holding instrument and the guiding pike are now removed, and the small incision is closed with two or three sutures, and thus the operation is completed without an assistant other than the nurse who hands the instruments.

It is evident that this technique allows nailing not only of intracapsular fractures but also of a high percentage of intertrochanteric fractures. The slanting position of the nail is stable enough, and an angled Jewett nail is not necessary in most cases. Thereby the very large incision necessary for the insertion of the angled Jewett nail may be supplied by the small incision sufficient for the technique described above (Fig. 6).

Figure 7 shows as an example a case of bilateral fracture of the neck of the femur, caused by electric convulsion therapy, in which the entire operation was done in 20 minutes by two surgeons, one working on each side.

CROSS CIRCULATION FOR INTRACARDIAC SURGERY

JAMES L. SOUTHWORTH, M.D.
AND
E. CONVERSE PEIRCE II, M.D.
BALTIMORE

THE PROCEDURE for extracorporeal circulation to be described is a relatively simple operation in which one animal (donor) provides the functions of the heart and lungs for himself and for a second animal (recipient) as well. By means of cross circulation an adequate supply of oxygenated blood is delivered to the recipient in order that the heart may be bypassed either in whole or in part, thus making experimental intracardiac surgery possible in laboratories where a mechanical heart or heart-lung is not at hand. It is the purpose of this paper to present the details of a workable cross circulation together with the results in an initial 20 pairs of dogs in which the left heart was bypassed.

METHOD

Healthy mongrel dogs at least 15 kg. in weight are chosen, a larger dog serving as donor for a smaller one when possible. Sodium pentobarbital is used for anesthesia; the donor is given positive-pressure oxygen during the actual shunting procedure while the recipient is similarly artificially ventilated during the entire time the chest is open. Arterial and venous pressures are measured by suitable manometers or by strain gages and a Brush analyzer and recorder. Electrocardiograms have been made in a number of experiments. The animals are given sodium heparin, 150 units per kilogram, before insertion of cannulas. At the termination of cross circulation, protamine sulfate [1] is given, the dosage of which is controlled by watching bleeding from the incisions rather than by measuring clotting time. On the average, 0.5 mg. per kilogram of protamine is satisfactory. This dose is on the low side of the theoretic requirement and is repeated after 20 minutes if no clotting is observed. In a number of the experiments free plasma hemochromogen was measured preoperatively and postoperatively by the method of Hunter and others [2] without taking into account the hemochromogen which might have been added by transfusion. Five hundred cubic centimeters of blood is usually given to one of the dogs during the cross circulation to cover loss from the open heart and accumulated operative losses. Additional blood is given if loss is severe, the blood pressures being used as an index of need. Occasionally at the conclusion of an experiment it is necessary to support the recipient's blood pressure at the expense of the donor, and this is done by transfusing the recipient through the arterial connections (with the venous connections occluded) before the tubes are disconnected.

From the Cardiovascular Clinic and the Surgical Service, Public Health Service Hospital.

The protamine (salmine) sulfate was kindly furnished by the Medical Department of Eli Lilly & Company.

1. Parkin, T. W., and Kvale, W. F.: Neutralization of the Anticoagulant Effects of Heparin with Protamine (Salmine), Am. Heart J. **37**:333, 1949.

2. Hunter, F. T.; Grove-Rasmussen, M., and Soutter, L.: A Spectrophotometric Method for Quantitating Hemoglobin in Plasma or Serum, Am. J. Clin. Path. **20**:429, 1950.

Most of our experience has been with bypassing the left heart.[3] The femoral vessels of the donor are exposed bilaterally for cannulation. The recipient's left chest is opened, and the following vessels are exposed: left subclavian artery, origin of the right pulmonary artery, and the entire left main pulmonary artery. As shown in Figure 1, the circulatory systems of the two animals are connected as follows: (*a*) venous blood is taken from the recipient's left pulmonary artery and led to a Y tube which is in turn connected to both femoral veins of the donor; (*b*) both femoral arteries of the donor are cannulated, connected to a Y tube and led into the aorta of the recipient through the stump of the left subclavian artery; (*c*) provision is made to occlude temporarily the right pulmonary artery during the period of cross circulation. The cross circulation is started by occluding the right pulmonary artery with the temporary ligature. Crossing can be stopped at any time, provided the recipient's heart is not fibrillating, by loosening this temporary ligature. While the right pulmonary artery is occluded, however, systemic venous blood of the recipient flows as usual into the right side of the recipient heart but is diverted into the

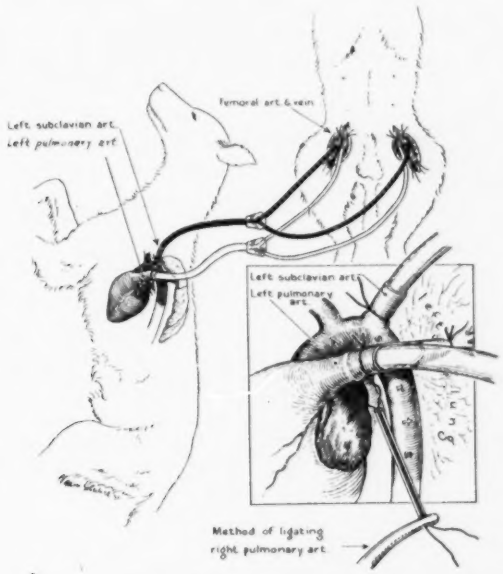


Fig. 1.—Arrangement of cannulas and tubing for cross circulation to bypass the left heart.

connecting tubes and into the systemic venous bed of the donor animal. Within the donor, blood flows in the normal circuit, but a portion of the systemic output is diverted through cannulas in the femoral arteries and, via the connecting tubes, flows into the aorta of the recipient. Ordinarily the recipient heart beats in a normal fashion; the recipient right heart is filled with blood and

3. To bypass the entire heart, the venae cavae of the recipient are cannulated with a Leeds cannula (Leeds, S. E.: Proc. Soc. Exper. Biol. & Med. **75**:468, 1950) which is attached to a Y tube with tygon tubing; the double side of the Y tube is led to both femoral veins of the donor. The donor's femoral arteries are cannulated and connected to a Y tube, the single side of which is led into the recipient's left subclavian artery. It has been possible to open either the right atrium or the right ventricle with survival and without undue loss of blood, but sometimes difficulty with venous return (from the recipient's venae cavae to the donor's femoral veins) is encountered during this operation. Our experience with this complete heart bypass operation has been limited, but it appears that it could be made to function more smoothly by adding a booster pump on the venous side of the circuit.

pumps blood into the donor. The recipient left heart contains only a small amount of blood which is probably derived from channels which open directly from the myocardial circulation into the left ventricle or possibly from bronchial vessels.

To discontinue the left heart bypass, the temporary ligature about the right pulmonary artery is first loosened, and the recipient animal is thereby allowed to resume his own circulatory and pulmonary functions. The recipient's left pulmonary artery is decannulated and reconstructed; the recipient's left subclavian artery stump is ligated. The femoral arteries and veins of the donor animal are ligated.

The sizes of cannulas and of connecting tubing are shown in the table. These sizes are not necessarily critical or ideal; for example, the internal diameter of the femoral artery cannulas is probably not the optimum one, but the external diameters are as large as they can be for insertion in animals of the size used in these experiments.

RESULTS

The following observations have been made during 20 operations (40 dogs) designed to provide access to the interior of the left heart of the recipient.

Location, Composition, and Approximate Diameters of Cannulas and Diameters of Tubing Employed in Cross Circulation *

	Donor Cannulas, Outside Diameters	Recipient Cannulas, Outside Diameters	Connecting Tubing, Inside Diameters
Venous circuit	Femoral veins polyethylene	Left pulmonary artery polyethylene	Tygon
	0.7 cm.	1.1 cm.	0.6 cm.
Arterial circuit	Femoral arteries glass	Left subclavian artery polyethylene	Tygon
	0.5 to 0.6 cm.	0.7 cm.	0.9 cm.

* The tubes are joined to the cannulas and the system filled with saline before cannulation; the lengths of the assembled venous and arterial circuits are 70 cm. each; total capacity is approximately 180 cc.

Survival.—Of 20 donors, 3 died. All three were lost because of hemorrhage due to technical errors. Two were lost early during attempts to put T tubes into the aorta; the 18th donor was lost in connection with an innovation in cannulation technic for recording blood pressure. Eleven of 20 recipients survived until they were killed or are now living. Of nine recipient dogs lost, the first five were lost owing to technical errors or prolonged heparin effect. With the sixth pair, the cannulation procedure was standardized and protamine reversal of heparin effect was begun. After this, 11 of 15 recipients survived. Of the four that died, one was lost owing to transfusion reaction several hours after surgery and three died from lesions of the mitral valve surgically produced. These three survived for some days, and their deaths were associated with attempts to produce chronic mitral stenosis experimentally.

Duration of Cross Circulation.—The length of time during which cross circulation was carried out varied from 10 minutes to more than one hour, being less than 25 minutes in only one instance. The chambers of the heart were open from 18 to 35 minutes. Operating time in the last five or six procedures was four hours for one hour of cross circulation time and 30 minutes' operating time within the heart. This seems to be the minimum time for the present team, which consists of two operators and one technician who serves as circulating nurse and anesthetist and for all other duties not requiring scrubbing.

Blood Pressure.—Blood pressure tracings from one experiment are shown in Figure 2. On the average the donor blood pressure has been 125 mm. mean and that of the recipient has been 70 mm. mean. The loss in pressure between the two varies with the length of tubing among other things. Neo-synephrine in doses of 0.5 to 1.0 mg. has been required at some time or other in every case during the period of crossing to maintain blood pressure. The drug, given intravenously to the donor, exerts its effect on the recipient in 22 seconds on the average. One to

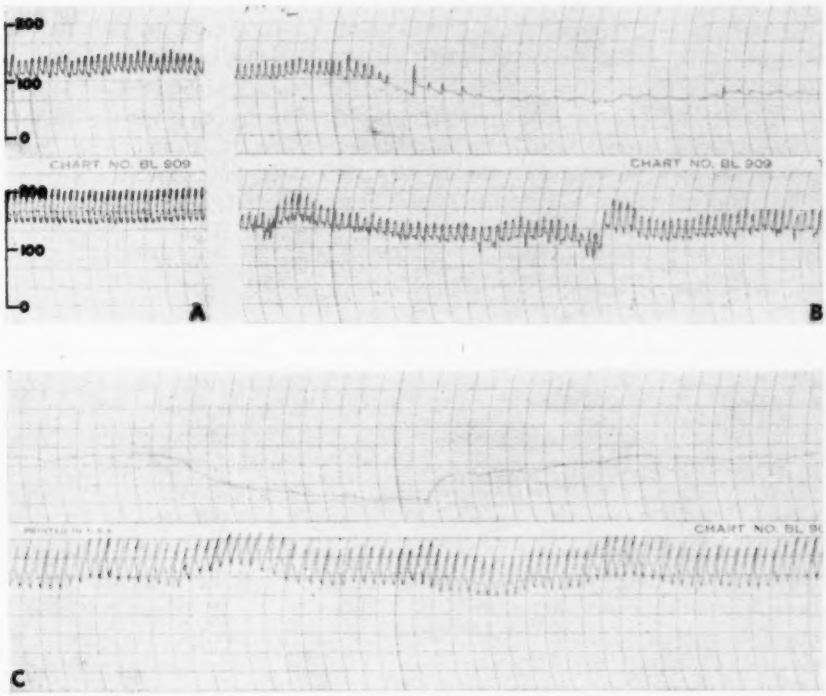


Fig. 2.—Blood pressures in recipient (upper tracings) and donor (lower tracings). *A*, before operation; *B*, at the beginning of cross circulation; *C*, during cross circulation. The dip in the recipient's pressure was produced by occluding the tubes to demonstrate dependence on the donor.

four such doses are required during an hour of cross circulation. It is obvious that cross circulation should not be attempted with a low-pressure donor animal.

Venous pressure in both animals remains normal unless ventricular fibrillation ensues.

Blood flow in the recipient is essentially nonpulsatile, as can be seen in Figure 2. Sometimes waves are impressed on this tracing by the recipient heart.

Hemolysis.—One recipient died after a hemolytic transfusion reaction. The postoperative free plasma hemochromogen was 324 mg. per 100 cc. The donor of this pair had only 96 mg. per 100 cc. of free hemochromogen postoperatively and sur-

vived. In the remainder, the levels for free hemochromogen were 0 to 5.0 mg. per 100 cc. preoperatively and 1.0 to 6.0 mg. per 100 cc. postoperatively. We have not endeavored to type dogs to prevent reactions.

Electrocardiograms.—Tracings taken during cross circulation showed no significant variations from normal.

Blood Loss.—Blood loss from the interior of the heart was measured roughly in some experiments: in the 12th pair, 75 cc. of blood was collected from the left atrium in 25 minutes; in the 13th pair, 200 cc. was collected from the left ventricle in 22 minutes; in the 19th pair, 90 cc. was collected from the left atrium in 20 minutes, and in the 20th pair, 35 cc. was collected from the left atrium in 5 minutes.

Exposure of the Interior of the Heart.—After we had gained sufficient experience to execute the procedure smoothly, it was possible to open either the left ventricle or the left atrium widely. The interior of the left ventricle can be seen clearly and the aortic valve with moderate difficulty. The aortic valve remains competent. The mitral valve flaps loosely when the left ventricle is empty, but as blood slowly collects in the ventricle the mitral valve becomes competent. Exposure of the atrium was adequate to permit making motion pictures of the mitral valve beating in situ without undue retraction.

Ventricular Fibrillation.—No instances of ventricular fibrillation were encountered among donors. This arrhythmia did not occur among recipients as a consequence of cross circulation alone; but it did result sometimes from manipulation of the ventricle, and sometimes it was deliberately induced to steady the heart for better operative exposure. Ordinarily the right heart of the recipient returns blood to the donor but blood pressure is maintained unchanged in the recipient if ventricular fibrillation occurs. This is associated with a rise in venous pressure in the recipient (typical example, from 4 to 29 cm. of saline). Occlusion of the right pulmonary artery is not necessary to maintain cross circulation when the recipient's heart is fibrillating if the heart is closed. Recipients with ventricular fibrillation have been maintained by cross circulation for periods up to 35 minutes without massage, with good coronary flow as evidenced by bleeding from the cut edge of the atrium and with survival. Ventricular fibrillation is tolerable, but whether it is safe or advisable to induce it in order to provide better exposure of the interior of the heart remains to be determined.

COMMENT

Cross circulation has been described by Jacobj,[4] Bazett and Quinby,[5] Firor,[6] and others, but not often at the high pressures and high rates of flow described here; we have not found a report of cross circulation designed to bypass the chambers of the heart to permit intracardiac operation. Firor's experiments[5] demonstrated

4. Jacobj, C.: Apparat zur Durchblutung isolirter überlebender Organe, Arch. exper. Path. u. Pharmakol. **26**:388, 1890.

5. Bazett, H. C., and Quinby, W. C.: A New Method for Crossed Circulation Experiments, with Some Observations on the Nature of Pressor Reflexes, Quart. J. Exper. Physiol. **12**:199, 1919-20.

6. Firor, W. M.: Experiments in Cross Circulation, Am. J. Physiol. **96**:146, 1931.

conclusively the practicability of mixing blood for prolonged periods in dogs. The extensive literature on exchange transfusion suggests that such mixing can be accomplished with reasonable risk in man.

Other operations with arrangements to provide external sources of circulation and oxygenation of blood, such as those pioneered by Gibbon,[7] Crafoord,[8] and Jongbloed,[9] have been reviewed by Karlson and his associates,[10] by Dennis and his colleagues,[11] and by other workers in this field. These methods have made use of pumps to serve as a heart and of filming mechanisms in an atmosphere of oxygen to oxygenate blood externally. A host of engineering problems are introduced by such an apparatus, but these have not been insurmountable, and it is probable that the mechanical heart-lungs are now, or soon will be, ready for use with patients. Experimentally, exposure of the interior of the left side of the heart is possible with procedures which employ a pump to maintain systemic circulation while the animal's own lungs oxygenate the blood. Wesolowski and others,[12] Kantrowitz and Kantrowitz,[13] and others have reported such procedures. These methods lack the advantage provided by external sources of circulatory and pulmonary function which permit the operator to deal with ventricular fibrillation with some degree of equanimity. The cross-circulation method has this important advantage and at the same time may be carried out without any very elaborate apparatus.

SUMMARY

A method is described for cross circulation in animals to provide access to the interior of the heart, and experience gained in 20 pairs of animals is given. With respect to the animal undergoing intracardiac operation, an external source of circulatory and pulmonary function is provided without need for an expensive machine.

NOTE.—After preparation of this paper, five additional left heart bypass operations have been conducted, with satisfactory results and with survival of all 10 animals.

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7. Gibbon, J. H., Jr.: The Maintenance of Life During Experimental Occlusion of Pulmonary Artery, Arch. Sug. **34**:1105, 1937. Gibbon, J. H., Jr., and Kraul, C. W.: An Efficient Oxygenator for Blood, J. Lab. & Clin. Med. **26**:1803, 1941. Gibbon, J. H., Jr.: Artificial Maintenance of the Circulation, Symposium, Surgery Study Section, Federal Security Agency, United States Public Health Service, Jan. 21, 1950.

8. Crafoord, C.: Some Aspects of the Development of Intrathoracic Surgery, Surg., Gynec. & Obst. **89**:629, 1949.

9. Jongbloed, J.: The Mechanical Heart-Lung System, Surg., Gynec. & Obst. **89**:684, 1949.

10. Karlson, K. E.; Dennis, C.; Westover, D., and Sanderson, D.: Pump-Oxygenator to Supplant the Heart and Lungs for Brief Periods: I. Evaluation of Oxygenator Techniques; An Efficient Oxygenator, Surgery **29**:678, 1951.

11. Dennis, C.; Karlson, K. E.; Eder, W. P.; Nelson, R. M.; Eddy, F. D., and Sanderson, D.: Pump-Oxygenator to Supplant the Heart and Lungs for Brief Periods: II. A Method Applicable to Dogs, Surgery **29**:697, 1951.

12. Wesolowski, S.; Miller, H. H.; Halkett, J. A. E., and Welch, C. S.: Experimental Replacement of the Heart by a Mechanical Extracorporeal Pump, Bull. New England M. Center **12**:41, 1950.

13. Kantrowitz, Adrian, and Kantrowitz, Arthur: Experimental Artificial Left Heart to Permit Surgical Exposure of Mitral Valve in Cats, Proc. Soc. Exper. Biol. & Med. **74**:193, 1950.

HISTOLOGY OF GOITER AND BLOOD IODINE

V. E. CHESKY, M.D.
W. C. DREESE, M.D.
B. O. DUBOCZKY, M.D.
AND
C. A. HELLWIG, M.D.
HALSTEAD, KAN.

TWENTY years ago we[1] studied the structure and function of goiter as observed in the Hertzler Clinic and, using the international classification of goiter, compared its histology with that described in other parts of the world (Table 1). From a study of 151 cases we concluded in 1929 that the goiter types in the Middle West were very different from those in mountainous regions of high endemicity. While Swiss surgeons see only 7% diffuse and 93% nodular goiters, we had 53% diffuse forms. While in Switzerland 70.7% of all goiters were fetal adenomas, only 13.9% of the surgical goiters in Kansas were of this type. Sixty-two per cent were colloid goiters, while Swiss surgeons report only 26.3%, and in Switzerland only 3% of all surgical goiters are toxic, compared with an incidence here of 65.6% (Table 2).

It became evident from these comparative studies that Middle Western types of goiter resemble more the forms found in the lowlands of Europe, i. e., Holland, Northern Germany, and the Russian plains. Since 1930 important changes have taken place in the prophylaxis and treatment of goiter which must have had a profound influence on its pathology. First, the prophylactic use of iodized salt has become almost general, and, second, since 1944 most patients with toxic goiter have received thiouracil previous to operation.

The present study was undertaken to find out whether the structure and function of goiter have changed after 20 years' use of iodized salt.

COMPARISON OF HISTOLOGIC TYPES OF SURGICAL GOITERS IN 1929 AND IN 1950

In our last series of 2,229 surgical benign goiters which were removed during the last 10 years at the Hertzler Clinic, 1,139 (51%) were diffuse and 1,090 (49%) nodular, i. e., about the same ratio as 20 years ago. Only 3% of the benign goiters during the last 10 years were fetal adenomas, against 11% in 1929, while colloid adenomas constituted 4% 20 years ago, but today constitute 31%. Colloid goiters, diffuse as well as nodular, accounted for 57% 20 years ago and today account for 70.2%. While in 1929 we found one lymphadenoid goiter among 151

From the Hertzler Clinic and Research Foundation.

1. Hellwig, C. A.: Form und Funktion des Nordamerikanischen Kropfes: Ein Beitrag zur geographischen Pathologie, Arch. klin. Chir. **154**:1-31, 1929.

TABLE 1.—*Classifications of Goiter*

International Classification	McCarrison (1927)	Marine (1927)	Hertzler (1929)	Rienhoff (1929)	MacCarty (1931)	Hertzler (1941)	Means (1948)	DeCourcy (1949)	American Association for Study of Goiter
A. Diffuse	....	....	....	....	A. Thyroid-shaped	....	....	....	....
Congenital diffuse goiter	Congenital goiter	Simple congenital goiter	....	....	....	....	....	....	....
Small-follicle goiter	Parenchymatous goiter	Hyperplasia and hypertrophy	....	....	....	....	....	....	....
Diffuse colloid goiter	Diffuse colloid goiter	Involution (colloid goiter)	Uniform stage of colloid goiter	Simple colloid goiter	Hypertrophic colloid goiter	Simple colloid goiter	Diffuse colloid goiter	Diffuse and simple colloid goiter	Diffuse nontoxic goiter
Exophthalmic goiter	Hyperplastic goiter	Exophthalmic goiter	Exophthalmic goiter	Hypertrophy and hyperplasia of the thyroid	Hypertrophic parenchymatous goiter	Diffuse toxic goiter	Diffuse toxic goiter	Diffuse toxic goiter	Diffuse toxic goiter
Lymphadenoid goiter	....	....	....	....	....	Thyroiditis	Hashimoto type of thyroiditis	Hashimoto's disease	....
B. Nodular hyperplasia	....	....	....	....	....	....	....	....	....
C. Nodular goiter	....	....	....	....	B. Nodular goiter	....	....	Adenomatous goiter	....
Fetal (small-follicle) adenoma	Adenoma	Nodular hyperplastic stage	Mixed tumor (fetal adenoma)	True benign parenchymatous neoplasm of the thyroid	Adenomatous goiter without parenchymatous hypertrophy	Fetal adenoma	Microfollicular adenoma	....	Nodular nontoxic goiter
Colloid adenoma								....	Nodular toxic goiter
Multinodular colloid goiter	Colloid adenoma	Nodular involutionary (colloid) stage	Bosselated stage of colloid goiter	Nodular colloid goiter	Nodular colloid goiter	Nodular goiter	Macrofollicular nodules	....	....

cases, in our recent series of 2,229 goiters 146 were diagnosed histologically as lymphadenoid (Hashimoto), an incidence of 6.6% of all goiters and 12.7% of the diffuse goiters (Table 3).

The most striking difference between the two series, therefore, is the increase in colloid goiter, especially the solitary colloid adenoma, while the incidence of fetal adenoma has markedly decreased. In our opinion this difference is caused by the widespread use of iodized salt, and it agrees well with goiter experiments in animals.

Marine [2] contended that colloid goiter does not develop from a normal gland by overproduction of colloid but that the thyroid enlargement is always initiated as

TABLE 2.—*Geographic Pathology of Benign Goiter*

	Switzerland (Per Cent)	Middle West (Per Cent)
Colloid goiter	26	70
Exophthalmic goiter	3	21
Fetal adenoma	71	3
Lymphadenoid goiter		6

TABLE 3.—*Histological Types of Benign Goiters in Middle West*

	1929 (Per Cent)	1950 (Per Cent)
Diffuse colloid goiter	17	10
Exophthalmic goiter	32	21
Lymphadenoid goiter	1	6
Nodular colloid goiter	36	29
Colloid adenoma	4	31
Fetal adenoma	11	3
Colloid goiter	57	70.2

an active hypertrophy and hyperplasia. He regards diffuse and nodular colloid goiter as an involutional stage of hyperplastic goiter. Accepting Marine's view, many writers regard goiters rich in colloid as having low thyroid function. This opinion is contrary to the results of animal experiments and clinical observation.

By the use of a positive goitrogenic factor, for instance a calcium-rich diet, goiters can be easily produced in white rats. These goiters vary in structure according to the amount of iodine contained in the diet.[3] The experimental goiters have small hyperplastic acini when calcium excess is combined with a low iodine content of the food; on the other hand, colloid goiters can be produced in white rats when the same high-calcium diet is given with an iodine supply 10 times larger than the

2. Marine, D.: Studies on Etiology of Goiter Including Graves' Disease (McBride lecture), Ann. Int. Med. **4**:423-432, 1930.

3. Hellwig, C. A.: Thyroid Adenoma in Experimental Animals, Am. J. Cancer **23**:550-555, 1935.

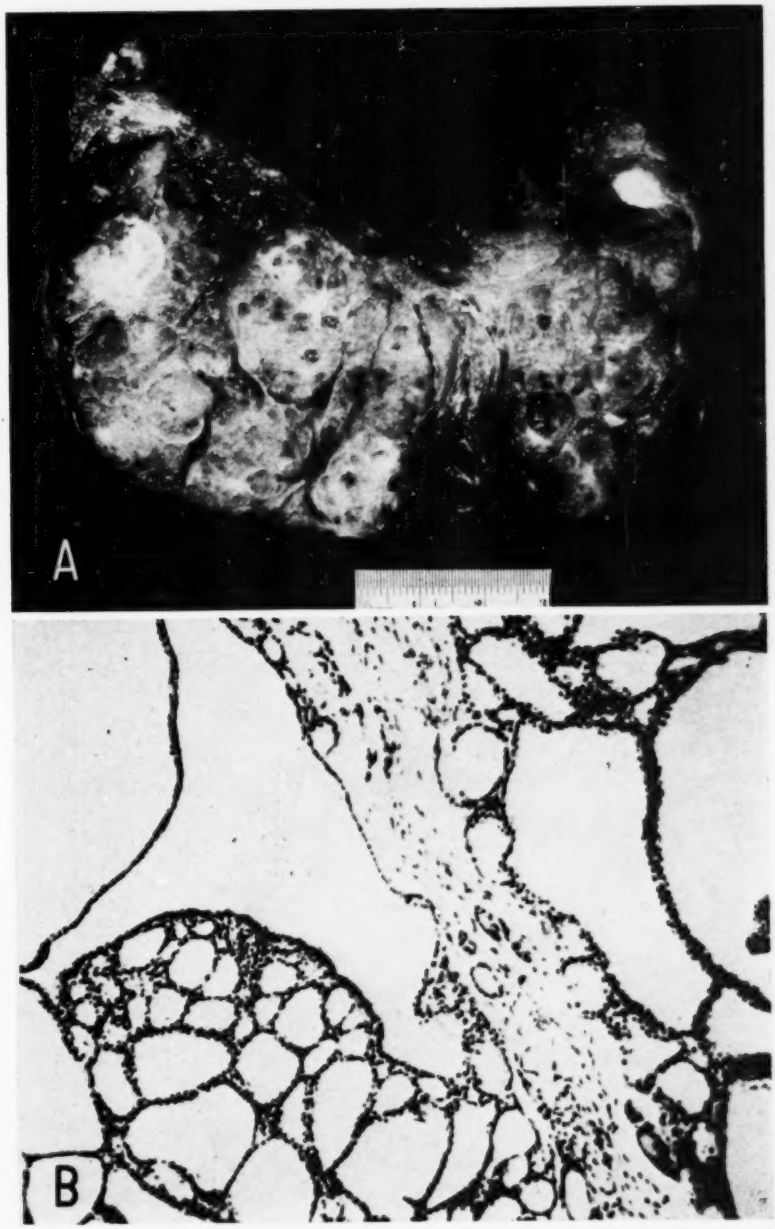

Fig. 1.—*A*, multinodular colloid goiter. Both lobes are composed of many small nodules. *B*, large colloid-filled follicles are lined with cuboid epithelium. In cushion-like elevation of wall new formation of acini takes place; × 120.

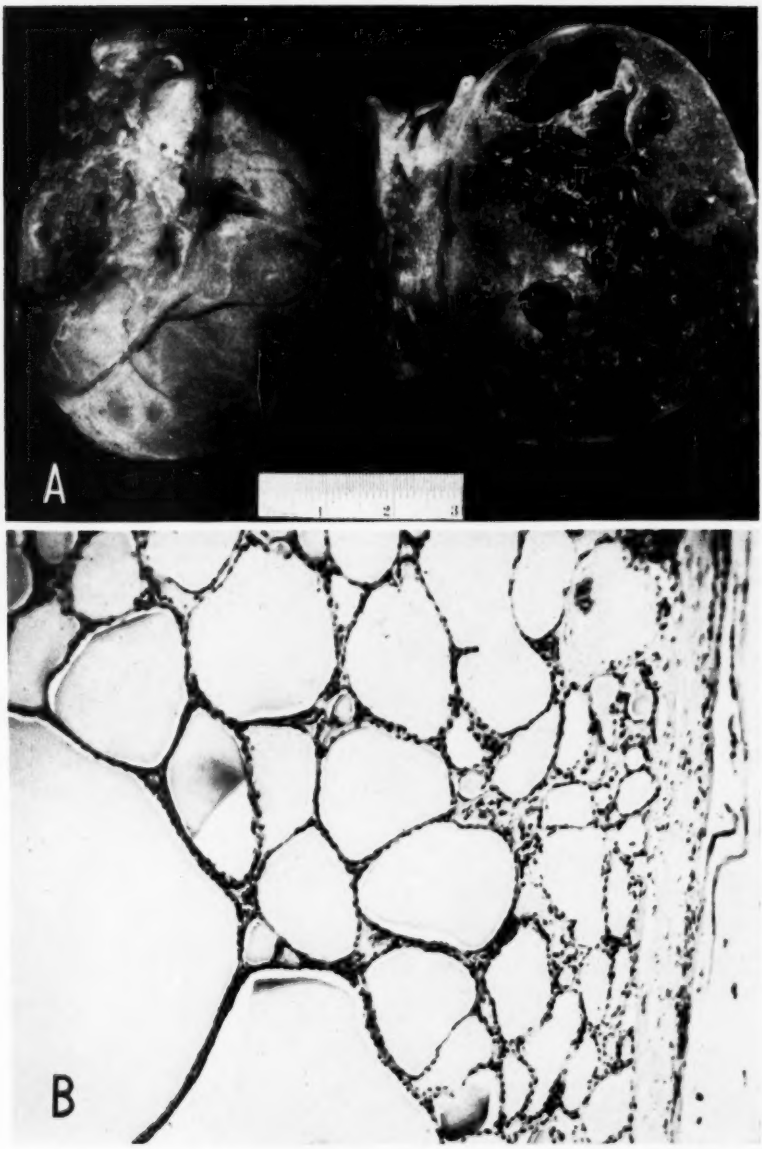

Fig. 2.—*A*, solitary colloid adenoma. The adenoma shows cystic and hemorrhagic areas. The fibrous capsule is distinct. *B*, large follicles with cuboid epithelium and abundant colloid; × 120. This type of goiter is much more frequent today than it was 20 years ago, before the introduction of iodized salt.

physiological requirement. Functionally, the experimental colloid-rich goiters are more active than are the colloid-poor hyperplastic goiters. These experimental data are in accord with epidemiological studies. In North America, where colloid goiter is the prototype of endemic goiter, hyperthyroidism is much commoner than in Switzerland, where the colloid-poor fetal adenoma is the commonest goiter type, often associated with hypothyroidism and cretinism.

After 20 years of goiter prophylaxis, the incidence of colloid adenomas has increased in our region from 4 to 31%, and that of colloid-poor fetal adenomas has decreased from 11 to 3%. This fact can best be explained by assuming that in goiter regions there must be a positive goitrogenic factor present and that the colloid content of endemic goiter varies, depending on the different iodine content of the food.

The functional value of the different goiter types in our 1929 series was based on the basal metabolic rate as the main laboratory test. In the present study we had at our disposal a much more reliable functional test, i. e., the determination of blood iodine.

BLOOD IODINE: MATERIAL AND METHODS

Routine iodine determinations have been made on our goiter patients since December, 1949. First we used a modified Salter's ashing method,[4] and later we followed Barker's distillation and ashing method.[5] After performing over 400 tests we found Barker's ashing method the most practical and reliable for clinical work.

The procedure as used in our laboratory differs from the original method of Barker in some details of the technic and in the calculation of the iodine content. We determine the total iodine content of each serum, as well as the protein-bound iodine (PBI). A high total iodine content reflects only a high iodine intake. We add 0.5 cc. of 12% aminoacetic acid (glycocoll) to two blank tubes before drying in order to have the same organic content as that in the serum tubes. Thus the same conditions for ashing are assured as those which influence the colorimetric reading. Two blanks are made for every ashing process. In dissolving the ash we add the water first and then the acids, in order to prevent formation of a slight opalescence which remains in the total iodine tubes even after centrifugation. For the colorimetric determinations of the iodine we use a Coleman junior spectrophotometer and 15 by 125-mm. colorimeter tubes. The reading and calculation are made on a linear scale.

The colorimetric procedure is carried out as follows. In order to prepare solutions for a standard curve, the ash solutions are centrifuged and the clear supernatant fluid of the two blanks are mixed together. Into each of four colorimeter tubes 3 cc. of this solution are pipetted. Then to the first tube 1 cc. of distilled water is added; this will be the reagent blank. To the other three tubes 0.42, 0.64, and 0.86 cc. of the working iodine solution, prepared from the dilute stock iodine solution (1:5), and 0.58, 0.36, and 0.14 cc. of distilled water are added, respectively. These amounts of iodine give 4, 6, and 8 γ, respectively. Three cubic centimeters of the supernatant fluid of each serum sample are pipetted in other colorimeter tubes, and 1 cc. of distilled water is added to bring them to the same volume. After 0.5 cc. of arsenious acid solution is added to all tubes they are placed in a 40 C. water bath for 10 minutes. Then 1 cc. of ceric ammonium sulfate solution, also warmed in the bath, is added to each tube at successive 45 or 30-second intervals, and after a rapid mixing an immediate colorimetric reading is made

4. Chesky, V. E.; Dreese, W. C.; Duboczky, B. O., and Hellwig, C. A.: To be published.

5. Barker, S. B.: Determination of Protein-Bound Iodine, J. Biol. Chem. **173**:715-724, 1948. Barker, S. B., and Humphrey, M. J.: Clinical Determination of Protein-Bound Iodine in Plasma, J. Clin. Endocrinol. **10**:1136-1141, 1950. Barker, S. B.; Humphrey, M. J., and Soley, M. H.: The Clinical Determination of Protein-Bound Iodine, J. Clin. Invest. **30**:55-62, 1951.

on each tube. A second reading is made at exactly 12 minutes after the addition of the seric solution. The difference between the first and second readings gives the colorimetric value.

If the colorimetric reading falls within the normal range, the iodine percentage may be read directly from the values of the standard solutions. If the readings are above the normal range, the iodine percentage is calculated from the following equation: The number of micrograms in the highest standard solution (St) is related to its second colorimetric reading (r 2) minus its first colorimetric reading (r 1) as the number of micrograms in the serum sample (x) is related to its second colorimetric reading (R 2) minus its first colorimetric reading (R 1).

$$\text{Equation:}\quad \frac{\gamma\, x}{R\,2 - R\,1} = \frac{\gamma\, St}{r\,2 - r\,1}$$

Example: St = 8 γ, r 1 = 11, r 2 = 30; $\frac{x}{36} = \frac{8}{19}$

Patient Serum = x, R 1 = 10, R 2 = 46; $x = 15.1\,\gamma$

If the colorimetric reading is below the normal range, the iodine percentage is calculated by comparison with the lowest standard.

When the iodine content of the sample is very high and the colorimetric reading at 12 minutes is over 80, the colorimetric procedure must be repeated with a smaller quantity of the remainder of the serum sample solution. Three tenths of a cubic centimeter of this solution is pipetted into another colorimetric tube, and the volume is brought up to 3 cc. with the following blank solution containing all the reagents: 1 cc. of 4 N sodium carbonate, 2 cc. of 2 N hydrochloric acid, 2 cc. of 7 N sulfuric acid and 2 cc. of distilled water. From this point on the procedure is described as above, and the result is multiplied by 10. If the 12 minute reading is again over 80, the process is repeated, using 0.03 cc. of the solution of the serum sample, and the result is multiplied by 100.

Our normal range of PBI obtained from 182 controls on patients without thyroid disorders varied between 4 and 8 γ per 100 cc., averaging 5.3 γ per 100 cc.; values below 3 γ are regarded by us as a definite indication of myxedema, and values above 8 γ indicate hyperthyroidism.

As well as can be judged from the literature, most laboratories determine only the PBI for clinical use. We feel, however, that the determination of total blood iodine should be included in every case. Patients with goiter enter our clinic often without knowing whether they have previously received iodine-containing medicine. Taurog and Chaikof[6] observed a linear increase of total iodine in blood plasma following iodine administration to rats. Protein-bound iodine increased when the daily intake rose from 2 to 78 γ; a further increase in iodine intake did not significantly influence the level of PBI. Danowski and his co-workers,[7] in clinical cases, found that administration of inorganic iodine in smaller doses (from 0.2 to 0.6 gm. of potassium iodide daily) produced not only a high elevation in total iodine but also a definite increase in PBI, which sometimes rose above the normal range. If large amounts of inorganic iodine are given, from 3 to 7 gm. daily, the total iodine may reach concentrations as high as 22,200 γ per 100 cc. and the PBI may rise from 12.4 to 31.8 γ per 100 cc. On the other hand, the thyroxine level of the plasma remained essentially unchanged.

According to Starr and his co-workers,[8] the PBI will increase to a level as high as the total blood iodine after administration of diagnostic roentgenographic dyes containing iodine and of

6. Taurog, A., and Chaikof, J. L.: Relation of the Thyroxine Content of the Thyroid Gland and of the Level of Protein-Bound Iodine of Plasma to Iodine Intake, J. Biol. Chem. **165**:217-222, 1946.

7. Danowski, T. S.; Johnston, S. Y., and Greenman, J. H.: Alterations in Serum Iodine Fractions Induced by the Administration of Inorganic Iodine in Massive Dosage, J. Clin. Endocrinol. **10**:519-531, 1950. Danowski, T. S.; Mateer, F.; Weigand, F. A.; Peters, J. H., and Greenman, J. H.: Serum Iodine Fractions in Subjects Receiving Potassium Iodide in Small Dosage, J. Clin. Endocrinol. **10**:532-539, 1950.

8. Starr, P.; Petit, D. W.; Chaney, A. L.; Rollman, H.; Alken, J. B.; Jamieson, B., and Kling, I.: J. Clin. Endocrinol. **10**:1237-1250, 1950.

iodine-containing amebacides and also after administration of sodium-5-iodo-thiouracil. This increase may last weeks or many months.

We agree with Danowski that the determination of thyroxine will overcome some of these diagnostic difficulties. From our series of cases in which we determined thyroxine also, it appears that it does not increase in the blood after inorganic iodine has been given to the patient. Organic x-ray dyes, however, will also increase the values of thyroxine, and therefore any blood iodine determination in cases in which these have been used is useless.

FINDINGS

Ninety-six unselected surgical patients who received no medicine for goiter before entering our clinic form the basis of the present iodine study (Table 4).

Twenty of the patients were men and 76 women. The youngest of this series of surgical patients was 19 years of age, the oldest was 74, and the average age was

TABLE 4.—*Data on Ninety-Six Patients Undergoing Iodine Study.*

Histological Diagnosis	No. of Cases	Sex		Average Age, Yr.	Ranges of PBI (γ %)	Average PBI, γ %	Clinical Diagnosis				
							Diffuse Goiter		Nodular Goiter		
		M	F				Non-toxic	Toxic	Non-toxic	Toxic	Malignant
Diffuse Goiter											
Diffuse colloid goiter	1	..	1	46.0	10.2	....	..	1	..	..	..
Lymphadenoid (Hashimoto)	7	..	7	50.5	4.5-5.5	4.7	..	..	7	..	..
Exophthalmic goiter	17	7	10	37.4	8.6-20.0	11.7	..	16	..	1	..
Nodular Goiter											
A. Solitary Adenoma											
Fetal adenoma (microfollicular)	5	2	3	43.6	3.2-6.2	5.1	..	..	5	..	..
Solitary colloid adenoma (macrofollicular)	21	4	17	43.8	4.0-10.1	5.9	..	..	18	3	..
Mixed solitary adenoma (micro-macrofollicular)	5	3	2	53.2	4.1-6.4	4.9	..	..	5	..	..
B. Multinodular Goiter											
Multinodular colloid goiter	20	3	17	53.2	4.0-14.0	7.5	..	1	13	6	..
C. Combination Form of Goiter											
Fetal adenoma and nodular colloid goiter	1	..	1	43.0	4.5	4.5	..	..	1	..	..
Colloid adenoma and diffuse colloid goiter	5	..	5	49.8	3.5-18.0	8.0	..	1	4	..	..
Colloid adenoma and multinodular colloid goiter	4	..	4	45.0	4.4-8.3	6.9	..	3	1	..	..
Malignant Thyroid Tumor											
Hürthle cell tumor	2	..	2	53.2	4.6-5.2	4.9	..	..	2	..	..
Adenocarcinoma	8	1	7	41.8	3.2-6.2	4.4	..	..	4	..	4
Total	96	20	76				22	60	10	4	

46.6. Seventy-four of the patients were from Kansas and 22 from the surrounding states.

The interval between the blood iodine determination and operation was within one week in 49 cases, between one and four weeks in 32 cases, from one to two months in 12 cases, and more than two months in three cases.

After iodine determination 35 of the patients needed preoperative treatment. Eleven were given propylthiouracil, 10 were given Lugol's solution, and 14 were given both.

Seventeen patients whose surgical specimens were found to be typical exophthalmic goiters on microscopic examination had a PBI level varying between 8.6 and 20 γ. The average was 11.7 γ. In 16 of these patients the condition had been diagnosed clinically as diffuse toxic goiter and in one as nodular toxic goiter. The only diffuse colloid goiter in our series was from a patient for whom a diagnosis of diffuse toxic goiter had been made. The patient was 46 years old and had a PBI level of 10.2 γ.

Seven of our patients had lymphadenoid goiter (Hashimoto). The preoperative diagnosis in all cases was nodular, nontoxic goiter. In the 7 patients the PBI content varied between 4.5 and 5.5 γ, the average being 4.7 γ.

Only five patients of this series had fetal adenomas with small follicles or with trabecular structure. There were no toxic symptoms present, and the value for PBI varied between 3.2 and 6.2 γ, while the average was 5.1 γ. The solitary colloid-rich, large-follicle adenoma was seen much more frequently, namely, in 21 patients, three of whom presented definite toxic symptoms. The PBI in these cases was higher than in fetal adenomas; it varied from 4.0 to 10.1 γ, the average being 5.9 γ.

While solitary colloid adenomas were seen in 21 of our patients, multinodular colloid goiters were present in 20. The PBI varied in this group between 4.0 and 14.0 γ. The average was higher in multinodular colloid goiter than in any other nodular goiter type, i. e., 7.5 γ. In one of these cases a clinical diagnosis of diffuse toxic goiter had been made, and the PBI value was 13.5 γ. In six patients with multinodular colloid goiter the clinical diagnosis was nodular toxic goiter, and the PBI ranged between 5.2 and 14.0 γ, the average being 8.6 γ. In 13 cases of this goiter type a clinical diagnosis of nontoxic nodular goiter was made; the PBI varied between 4 and 7 γ, and the average was 5.2 γ. There were 10 patients with malignant goiters in our series. They had the lowest iodine levels in the blood, with an average of 4.6 γ.

We did not include the combination forms of goiter in our study as the varied histologic structure of these goiters made a comparison between structure and function uncertain.

From our comparative histophysiologic study using the PBI level as a functional goiter test it becomes evident that the colloid-poor fetal adenoma, malignant goiter, and lymphadenoid goiter are associated with a PBI level lower than the normal average (5.3 γ). On the other hand, exophthalmic goiter, nodular and diffuse colloid goiter are associated with a PBI value exceeding the normal average.

Comparison of Blood Iodine Level and Other Laboratory Tests for Thyroid Function.—We found that there was a good correlation between basal metabolic rate and PBI. The difficulty of obtaining true values for basal metabolism due to incomplete relaxation of the patient has been stressed repeatedly. This is the principal reason that we appreciate determination of the PBI as a clinical laboratory test which demands only a sample of blood, even though the technic is tedious and time-consuming. Salter and his co-workers,[9] Riggs,[10] Rapport and Curtis,[11] Barker, and others have stressed the greater reliability of the PBI level over the basal metabolic rate and have attributed it to the greater objectivity of the chemical determination. The principal limitation of the PBI test in patients who have received inorganic iodine may be overcome by simultaneous determination of thyroxine.

In general the PBI values are highly correlated with the severity of clinical symptoms. Of the 32 toxic patients, 9 were considered to have mild thyrotoxicosis

9. Salter, W. T.; Bassett, A. M., and Sappington, T. S.: Protein-Bound Iodine in Blood: VI. Its Relation to Thyroid Function in 100 Clinical Cases, Am. J. M. Sc. **202**:527, 1941.

10. Riggs, D. S.: Serum Protein-Bound Iodine as a Diagnostic Aid, Tr. Am. A. Study Goiter, pp. 137-144, 1947.

11. Rapport, R. L., and Curtis, G. M.: The Clinical Significance of the Blood Iodine, A Review, J. Clin. Endocrinol. **10**:735-790, 1950.

and 23 severe thyrotoxicosis. In the first group the average PBI value was 8.4 γ, against 11.8 γ in the group with severe clinical symptoms. We found that blood cholesterol determinations were of little value in the cases of hyperthyroidism. On the other hand, in myxedema we always found values above 300 mg. per 100 cc.

CONCLUSIONS

1. Comparison of the different types of surgical goiter before and after 20 years of goiter prophylaxis reveals a marked increase of colloid goiter. The incidence of small-follicle fetal adenomas has decreased from 11 to 3% of the benign goiters, while that of solitary colloid adenomas has increased from 4% in 1929 to 31% in 1950.

2. The relative increase of colloid goiters in surgical material after iodine prophylaxis can be best explained by the presence of a positive goitrogenic factor which produces different types of goiter dependent on the iodine content of the food.

3. Blood-iodine studies indicate that colloid adenomas have a higher functional value than colloid-poor adenomas.

4. With the exception of exophthalmic goiters, the highest blood-iodine values were found associated with diffuse and multinodular colloid goiters.

ANEURYSM OF AN ANOMALOUS PANCREATICODUODENAL ARTERY

Case Report and Review of the Literature

JAMES W. SAMPSEL, M.D.
FRANK M. BARRY, M.D.
AND
HOWARD D. STEELE, M.D.
CLEVELAND

ANEURYSMS of intra-abdominal vessels other than the aorta are rare surgical lesions. The hepatic artery or its branches has been the site of these aneurysms in 85 cases collected by Malloy and Janson [1] in 1942, and since that time nine cases have been added.[2] It is the object of this report to present such a lesion discovered at operation and proved to arise from an anomalous pancreaticoduodenal artery at autopsy. We will also briefly review pertinent points from the literature.

REPORT OF A CASE

C. R., admitted to the hospital on July 19, 1950, was a 68-year-old white farmer with a six-week history of painless jaundice, pruritus, acholic stools, and dark-colored urine. In the 18 years before his admission he had intermittent "attacks" of jaundice that occurred on approximately seven occasions, but this last episode was most severe, and he was advised by his physician to seek hospitalization. A weight loss of 8 lb. (3.6 kg.) had occurred in the last six weeks.

Physical Examination.—Temperature was 37.5 C. (99.5 F.), pulse rate 68, respiration 16, and blood pressure 120/88. There was marked dark yellow coloring throughout the skin and sclerae. Scratch marks were present over most of the body. A few dry rales were present at the left base and a blowing systolic murmur at the cardiac apex. The abdomen was protuberant, and the liver was palpable 4 cm. below the costal margin. Its edge was round, smooth, and somewhat tender. An indefinite mass was present, approximately 8 cm. in diameter, located just to the right of the umbilicus.

Laboratory Findings.—The hemoglobin was 76%, and the white blood cells numbered 7,600. The urine was dark brown, with a specific gravity of 1.013. The blood urea nitrogen

From the University Hospitals of Cleveland.

1. Malloy, H. R., and Janson, R. S.: Aneurysm of the Hepatic Artery, Am. J. Surg. **57**:359-363, 1942.

2. (*a*) Volini, I. F., and Popper, H.: Saccular Aneursym of Left Branch of Hepatic Artery, S. Clin. North America **28**:267-274, 1948. (*b*) Taylor, C. E.: Ruptured Anastomotic Aneurysm of Gastric Arteries: Case Report and Review of Literature, Am. J. Surg. **68**:258-260, 1945. (*c*) Donaldson, G. A., and Hamlin, E.: Massive Hematemesis Resulting from Rupture of Gastric-Artery Aneurysm, New England J. Med. **243**:369-373, 7, 1950. (*d*) Grant, J. L.; Fitts, J. T., Jr., and Raudin, I. S.: Aneurysm of the Hepatic Artery: Report of 2 Cases and Consideration of Surgical Treatment, Surg., Gynec. & Obst. **91**:527-532, 1950. (*e*) McNamara, W. L.; Baker, L. A., and Costich, K.: Aneurysm of Hepatic Artery, Ann. Surg. **123**:427-434, 1946. (*f*) Taylor, G. G.: A Rare Cause of Severe Gastrointestinal Hemorrhage with a Note on Aneurysm of the Hepatic Artery, Brit. M. J. **1**:504-505, 1943.

was 8.3 mg. per 100 cc., fasting blood sugar 79 mg. per 100 cc., total serum protein 6.1 gm., and serum bilirubin 12.8 mg. direct and 20.13 mg. indirect. The alkaline phosphatase was 25.5 units, and the cephalin-cholesterol flocculation was negative.

Roentgen Study.—Preoperative roentgenograms of the upper gastrointestinal tract showed no evidence of active disease, and the duodenal loop was normal.

Operative Data.—The presumptive diagnosis was obstruction of the common duct by tumor. With the patient under gas-oxygen-ether anesthesia, the abdomen was opened through a right rectus incision. The liver was enlarged and showed a mild degree of cirrhotic change, probably obstructive in origin. The gallbladder was tense and not extremely enlarged, but the common duct was approximately 2 cm. in diameter and tortuous. There was a mass in the region of the head of the pancreas which was first thought to be carcinoma. To evaluate this mass, the duodenum and right colon were freed by cutting the lateral peritoneal reflection and getting the left hand behind these structures. The tumor was then palpated bimanually; it was a soft, rubbery, cystic mass with small areas of calcification. The lesion pulsated, and the

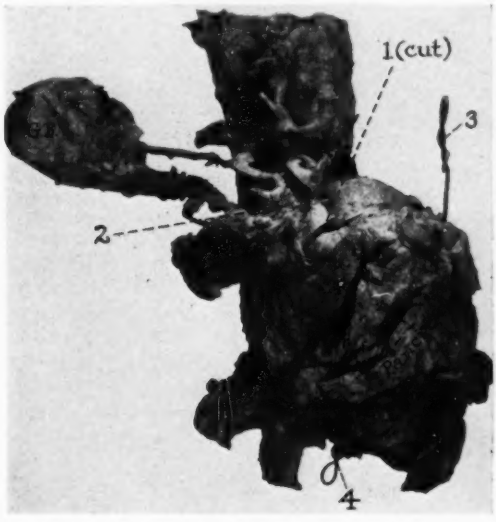

Fig. 1.—Photograph of autopsy specimen showing the Anterior surface of the mass. *1*, the true fusiform aneurysm in the pancreaticoduodenal artery, *2*, site of hepaticojejunostomy, *3*, probe in pancreatic duct, and *4*, probe in common hepatic duct. The main spurious aneurysmal mass is seen beneath pancreas and opened duodenum.

pulsation was expansile in all directions. It had a palpable and audible bruit. A needle was inserted into the mass, and it contained arterial blood. Clear white bile was obtained from an opening made in the distal end of the common hepatic duct, and palpation with the finger in the duct revealed the pulsating mass to be the obstructing tumor. It was interpreted as being an aneurysm within the pancreas, probably arising from the superior mesenteric artery, or possibly the inferior pancreaticoduodenal artery. The gall bladder was then opened, and it contained thick bile under low pressure with multiple mulberry calculi.

It did not seem wise to attempt resection of the mass; it was felt that the pancreas enveloped the aneurysm and further dissection would endanger the blood supply of the entire small intestine. The surgeon elected to do a hepaticodochoenterostomy and a Roux-Y loop formed with a side-to-end anastomosis between the common hepatic duct and the distal end of the jejunum.

Postoperative Course.—This was immediately complicated by prolonged hypotension and oliguria. The blood urea nitrogen rose to 150 mg. per 100 cc., and the general condition varied between semicoma and periods of irrational activity for eight days. Marked atelectasis and

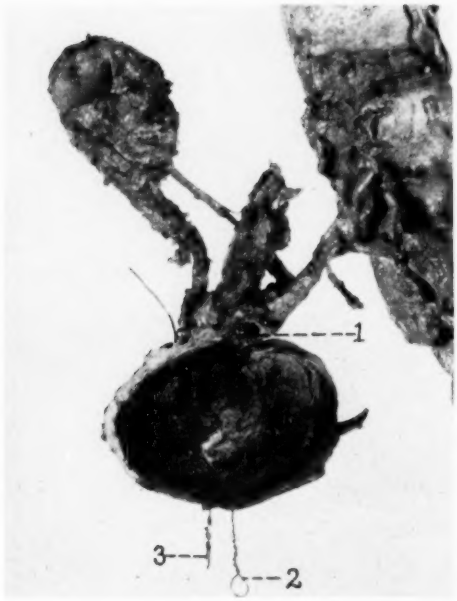

Fig. 2.—Cut surface of the lesion demonstrating (*1*) the communication between true and false aneurysm, (*2*) probe in cystic duct, and (*3*) probe in common hepatic duct. Both these ducts were occluded by pressure from the mass.

Fig. 3.—Low-power microscopic view to show the arteriosclerosis with calcification in the wall of the true aneurysm and the site of communication with a fibrous-walled false aneurysm.

probable bronchopneumonia developed. A cholangiogram, made several days after operation, demonstrated circular streaky shadows in the right side of the upper abdomen suggestive of aneurysm.

Another episode of weakness and hypotension was ascribed to a potassium deficiency on the 12th postoperative day. Two weeks later a right subphrenic abscess cavity was drained of 1,500 cc. of yellow pus that produced Escherichia coli when cultured. The general condition improved after this procedure, and the patient took food voluntarily for the first time. The serum bilirubin level was now down to 4.0 mg. per 100 cc., blood urea nitrogen was 47 mg., chlorides 142 mEq., and potassium 5.4 mEq.

After two more weeks of continued improvement, bright red blood began to appear on the abdominal wound dressing. The final episode occurred on the 56th hospital day. Sudden severe midabdominal pain developed, and there were vomiting of coffee-ground material and extreme restlessness accompanied with sudden irreversible shock.

Autopsy Findings.—The organs of the upper abdomen had modified relationships because of previous surgery, and a large mass was present in the region of the head of the pancreas. The preperitoneal cavity contained 650 cc. of fluid blood and clots; there was about 400 cc. of blood extravasated retroperitoneally in the right upper quadrant.

On close examination of the mass it was seen to displace the body of the pancreas anteriorly and inferiorly, while the first and second portions of the duodenum were anterior and slightly lateral to it. The bile ducts were compressed against its posterior aspect. The lesion was firm, rounded, measured 8 by 7 by 7 cm., and was continuous with the posterior aspect of a medium-sized artery, a direct branch of the hepatic, thought to be the pancreaticoduodenal. Beginning 1 cm. from the origin of this vessel from the hepatic artery there was an area of fusiform dilatation, a true aneurysm, 2.5 cm. in length and 1.2 cm. in diameter at its midportion. The small fusiform dilatation resided on the anterior surface of the large saccular mass, and a definite 3-mm. communication was demonstrated between the two. Section of the latter mass showed it to be a false aneurysm, 8 cm. in diameter, containing a well-demarcated outer fibrous layer with adjacent laminations and a central cavity filled with more recent blood clot. A ragged rupture was present in the large mass, 3 mm. in diameter, located superiorly, slightly posteriorly, and laterally, at a point where the bile ducts were compressed against the lesion.

The common hepatic duct was dilated to 5 cm. in circumference, and the jejunum was intactly anastomosed to it just proximal to the obstructing tumor. The cystic duct coursed around the posterior surface of the mass, paralleling the common hepatic duct. The two were obstructed, and they joined to form the common bile duct just 2 cm. from the ampulla.

Microscopic Observations.—The dilatation in the artery showed arteriosclerosis with calcification. The wall of the larger mass was dense fibrous connective tissue.

COMMENT

The aneurysm responsible for this patient's disability arose in a direct branch of the hepatic artery with terminal branches distal to the lesion distributed to the duodenum and the medial pancreas. The anomaly alone is not commonly seen. Lipshutz mentions the occurrence of the superior pancreaticoduodenal artery branching directly off the hepatic in only 3 of 85 complete celiac axis dissections.[3] The distribution of aneurysms throughout the hepatic artery and its branches in the 85 cases [1] has been the hepatic proper, 40; right branch, 26; left branch, 7; both right and left branches, 1; cystic artery, 3, and gastroduodenal branch, 1. Of the nine lesions recorded since this report, four were in the hepatic artery proper, one in the left branch, and four involved gastric branches. No previous case was discovered in which the origin was in the superior pancreaticoduodenal artery.

3. Lipshutz, B.: A Composite Study of the Cœliac Axis Artery, Ann. Surg. **65**:159, 1917.

The pathology, etiology, and treatment of these lesions are discussed at length in previous reviews.[4] By far their most important pathological feature is a tendency to rupture into the general peritoneal cavity or erode into an adjacent viscus to produce sudden or gradual hemorrhage. This rupture has occurred in approximately 74 of the 94 cases so far reported, and it was the cause of death in our patient. As mentioned, the general abdominal cavity has been the most frequent site of these hemorrhages, but they have also taken place into the extrahepatic bile ducts, duodenum, gall bladder, stomach, and portal vein. The aneurysms themselves have been of the true or false variety. True dilatations of the vessel wall are usually smaller in size, but the spurious aneurysms or hematomas attain larger size. The latter readily become adherent to surrounding structures and may cause compression of bile ducts.

A majority of these aneurysms seem to have their origin associated with an acute inflammatory process that involves the vessel wall by direct extension from some other focus or by infected emboli. Cholecystitis, pneumonia, osteomyelitis, endocarditis, and typhoid have been associated with the production of these defects in the vessel wall. Intimal and medial arteriosclerotic change formed the basis for our case, and pure arteriosclerosis is generally considered to be the second most frequent etiological factor. A definite causative factor was noted in 50 cases of Friedenwald,[4a] and in only 12 of these was arteriosclerosis involved. We feel that the latter factor can be implicated more frequently than this, especially in the recently occurring cases. Trauma, primary arterial disease such as periarteritis nodosa,[5] and congenital arterial defects[6] have been mentioned, but syphilis has proved the source of the disease rarely.

Abdominal pain, hemorrhage in the form of melena or hematemesis, and jaundice are the cardinal symptoms. The last is usually of the obstructive type. There are many cases without prodromal symptoms before sudden irreversible shock develops.[7] The cases of Donaldson and Hamlin[2c] are striking with massive hematemesis suspected of being caused by bleeding gastric ulcers. The diagnosis is suggested by a pulsating tumor in the right upper quadrant, exhibiting a systolic bruit.[8] Our patient had an indefinite palpable mass which was proved to pulsate and to have a bruit at operation. A plain roentgenogram is an aid to a positive diagnosis in the more commonly occurring aneurysms of the splenic artery,[9] and the fine streaky shadows discovered on our postoperative roentgenogram suggest that a plain abdominal film should be obtained in every suspected case.

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4. (*a*) Friedenwald, J., and Tannenbaum, K. H.: Aneurysm of Hepatic Artery, Am. J. M. Sc. **165**:11-28, 1923. (*b*) Weiss, E.: Aneurysm of Hepatic Artery, Am. J. M. Sc. **161**:859, 1921. (*c*) Rolland, W.: Aneurysm of the Hepatic Artery, Glasgow M. J. **69**:342-358, 1908. (*d*) McCrae, T.: Aneurysm of the Hepatic Artery: A Diagnostic Study, Internat. Clin. **3**:1, 1920.

5. Klotz, O.: Periarteritis Nodosa, J. M. Research **37**:1, 1917.

6. Shallow, T. A.; Herbut, P. A., and Wagner, F. B.: Abdominal Apoplexy Secondary to Ruptured Congenital Aneurysm, Surgery **19**:177-185, 1946.

7. Teacher, J. H., and Jack, W. R.: Aneurysm of the Hepatic Artery, Glasgow M. J. **86**:277, 1916.

8. Friedman, G. A.: A Tentative Diagnosis of Aneurysm of the Hepatic Artery and Findings at Operation, Med. Record **82**:522-525, 1942.

9. Lindboe, E. F.: Aneurysm of the Spenic Artery Diagnosed by X-Rays and Operated upon with Success, Acta chir. scandinav. **72**:108-114, 1932.

Ideally, some procedure should be attempted on these lesions whenever they are encountered at operation because of the high incidence of eventual perforation, with fatal hemorrhage. A palliative hepaticojejunostomy was selected in the instance reported here because it was felt that further attack on the lesion would endanger the superior mesenteric artery. Autopsy proved that the diseased vessel might possibly have been ligated close to its origin off the hepatic artery; this site was free of sclerosis, but at operation it was surrounded by dense fibrous adhesions. This difficulty of obtaining exposure in the presence of dense fibrous adhesions and surrounding vital structures will be a major limiting factor in many cases in which operation is performed. Only a few of these operations have met with success, one as a result of including a cirsoid gastric aneurysm in a resected stomach,[2e] the others as a result of ligations of the hepatic artery proper.[10]

Simple ligation of the offending artery has been suggested by many previous authors. This procedure combined with excision of the aneurysm, if possible, would suffice to abolish those peripheral lesions in the right or left gastric, cystic, or gastroduodenal vessels. Treatment of the condition occurring in the hepatic artery itself has been discussed at length by Grant and others.[2d] He suggests that ligation of the hepatic artery is not uniformly fatal if done proximal to the larger branches, i. e., the right gastric and the gastroduodenal branch. Newer suggestions for surgical therapy include reconstruction of the hepatic artery with grafts of artery or vein, employing anastomoses with a contiguous vessel that could be safely sacrificed, viz., splenic, right gastric, or gastroduodenal vessels. Perfusion of the liver with oxygenated blood[11] might be imperative during a time-consuming anastomosis, and massive doses of antibiotics postoperatively might help to prevent liver necrosis.[12]

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10. Allesandi, R., in Nelson's Loose-Leaf Living Surgery, New York, Thos. Nelson & Sons, 1932, vol. 5.

11. Frank, H. A.; Seligman, A. M., and Fine, J.: Traumatic Shock: The Prevention of Irreversibility in Hemorrhagic Shock by Vivi-Perfusion of the Liver, J. Clin. Invest. **25**:22-29, 1946.

12. Markowitz, J.; Rappaport, A., and Scott, A. C.: Prevention of Liver Necrosis Following Ligation of the Hepatic Artery, Proc. Soc. Exper. Biol. & Med. **70**:305, 1949.

SHOCK THERAPY WITH INTRAPERITONEAL INFUSION OF BLOOD VOLUME REPLENISHERS, DEXTRAN AND PVP

JOSEPH K. NARAT, M.D.

PHILIP A. CASELLA, M.D.
AND
JOSEPH P. CANGELOSI, M.D.

CHICAGO

ANIMAL experimentation [1] has established the fact that certain fluids, such as glucose or isotonic sodium chloride solution, are absorbed and well tolerated when administered by drip intraperitoneally. Subsequently, the efficacy of this method of administration of fluids was substantiated in a clinical study.[2] The growing interest in so-called plasma substitutes suggested the question of whether they also could be introduced intraperitoneally.

In recent years it has become increasingly apparent that in the event of a great military or civilian catastrophe the stockpiles of whole blood and plasma may not suffice and that there is an urgent need for other agents capable of replenishing the depleted stores of body fluids. The terms "plasma substitute" or "plasma expander" applied to such substances are misnomers, objectionable from the theoretical as well as the practical point of view. They are misnomers because, in contradistinction to plasma, such agents are deprived of certain biophysical and biochemical functions, such as furnishing essential nutrients, buffering action, transport and mobilization of antibodies, and protection against blood loss by components of the clotting mechanism. The terms are condemnable and should be banished from the medical literature as well as from the lay press because they threaten to create misconception among prospective blood donors by insinuating that whole blood is no longer necessary. Hence, the term "blood volume replenisher" or "blood volume expander" appears more appropriate as it describes the main, if not the only, function of such agents, namely, restoration and stabilization of blood volume.

None of the products hitherto proposed for this purpose is considered entirely free from objections, such as too low osmotic pressure, necessity of heating, creation of organic changes resembling lipidosis or amyloidosis, or potential hazards of a virus infection, agglutination, hemolysis or formation of antigens.

According to their origin, blood volume replenishers may be divided into four groups: (1) those of animal origin, such as human serum, serum albumin, despe-

Part of the expenses of this work was defrayed by a grant from Abbott Laboratories, North Chicago, Ill.

1. Narat, J. K.; Cipolla, A.; Cangelosi, J., and Vincenti, A. L.: Intraperitoneal Drip for Postoperative Administration of Fluids: Preliminary Report, Arch. Surg. **60**:102 (Jan.) 1950; Intraperitoneal Drip in Presence of Abdominal Distention, Am. J. Surg. **79**:439, 1950.

2. Narat, J. K., and Carton, A. K.: Intraperitoneal Drip After Laparotomies: Its Clinical Application, A. M. A. Arch. Surg. **62**:520 (April) 1951.

ciated bovine serum, ascitic fluid, gelatin or isinglass, (2) those of vegetative origin, such as gum acacia, pectin, algin, methylcellulose or a polysaccharide from okra, (3) synthetic products such as polyvinylalcohol or polyvinylpyrrolidone (PVP), and (4) biochemical products such as dextran. The last two, representing the latest additions to the family of blood volume replenishers, approach the ideal of a perfect replenisher closer than the other aforementioned agents.

PVP, first produced by Hecht and Weese,[3] is a synthetic colloid made by permitting formaldehyde to react with acetylene over a copper acetylide catalyst. This reaction is followed by hydrogenation, vinylation and polymerization. The empirical formula of PVP is $(C_6H_9NO)_n$, and its pH is 3.6 to 3.8. Dextran was discovered in 1869 by the German chemist Scheibler as a conaminant during beet sugar refining. It is a polydispersoid glucose polymer, synthesized microbiologically by the action of the organism Leuconostoc mesenteroides (Betacoccus arabinosaceus) on sucrose. Dextran molecule corresponds to the empirical formula $(C_6H_{10}O_5)_n$. A partially hydrolyzed colloidal dextran solution was introduced as a blood volume replenisher by Swedish investigators Grönwall and Ingelman.[4] Its pH is over 4.5.

Both products offer the following advantages: They (1) are virus-free, (2) do not lead to formation of antigens, (3) have viscosity and osmotic pressure similar to those of plasma, (4) are free of pyrogens, (5) are stable, (6) stand considerable variations in temperature, (7) do not require typing, crossmatching and the Kahn test, (8) are relatively inexpensive, (9) do not require refrigeration, and (10) lend themselves to large-scale production. On the other hand, they are not able to perform the nutritive, buffering or immunologic functions of plasma proteins.

The present investigation was undertaken to assess the value of intraperitoneal administration of PVP and dextran.[5] The study consisted of determination of tolerance of these agents by rats, rabbits, and dogs, the rate of absorption, investigation of their effect on blood and parenchymatous organs, and their value in combating hemorrhagic shock.

TECHNIC

A 3.5% solution of PVP in Ringer's solution and a 6% solution of dextran, as supplied by the manufacturers, were used for all injections.

The following methods were employed: Wintrobe and Landsberg's[6] for hematocrit determinations, Rourke and Ernstene's[7] for sedimentation rate, Kingsley's[8] for total protein and albumin-globulin ratio, Gregersen's T-1824 dye technic[9] for plasma volume, the method of Phillip and others'[10] for specific gravity of blood, and Schechter's[11] method for measuring the amount of peritoneal fluid. The Oswald viscosimeter was used for measurements of viscosity, and a

3. Hecht, G., and Weese, H.: München med. Wchnschr. **90**:11, 1943.

4. Grönwall, A., and Ingelman, B.: Acta physiol. scandinav. **7**:97, 1944.

5. PVP was supplied by Abbott Laboratories, North Chicago, Ill. Macrodex (trade name for dextran) was made available through the courtesy of Pharmacia Laboratories, Rochester, Minn.

6. Wintrobe, M., and Landsberg, J. W.: Am. J. M. Sc. **189**:102, 1935.

7. Rourke, M. D., and Ernstene, A. C.: J. Clin. Invest. **8**:545, 1930.

8. Kingsley, G. R.: J. Lab. & Clin. Med. **27**:840, 1942.

9. Gregersen, J. L.: J. Lab. Clin. Med. **29**:1266, 1944.

10. Phillips, R. A., and others: Bull. U. S. Army Dept. **71**:66, 1943.

11. Schechter, A. J.: Yale J. Biol. & Med. **4**:167, 1931.

University of Chicago type osmometer for measurements of colloidal osmotic pressure. Determinations of dextran contents of the blood were done according to the method described by Hint and Thorsen,[12] and PVP contents were measured by the technic suggested by Porter and Silber.[13] The method consists essentially of mixing the sample with methanol, centrifuging, adding sodium sulfate to supernatant fluid, and estimating the turbidity by determining light transmission in a Coleman universal spectrophotometer. PVP determination in the urine was accomplished by precipitation by means of trichloroacetic acid.

Hemorrhagic shock was created by graded bleeding of heparinized, unanesthetized dogs from an exposed femoral artery. Withdrawal of the amount of blood corresponding to from 3.5 to 4% of the body weight, or from 37 to 45% of the estimated blood volume, was required to obtain a stable blood pressure level of approximately 40 to 44 mm. of mercury, the percentages being calculated on the assumption that blood accounts for 9.5% of the body weight in grams. At this drastic level of hypotension the following clinical signs were usually observed: pallor of lips, air hunger, loss of sphincter control, and decline of body temperature. The importance of distinguishing between posthemorrhagic hypotension and hemorrhagic shock must be emphasized. As pointed out by Gregerson,[14] blood pressure alone is not a reliable index of the severity of shock. Reduction in blood volume is the initial and determining factor. Therefore the animal was considered as being in shock only if (1) it exhibited clinical signs, (2) the blood pressure was not higher than 44 mm. of mercury, and (3) the amount of blood withdrawn equaled at least 3.5% of the body weight or at least 37% of the estimated blood volume. Pseudoirreversible shock obtained in this manner constitutes that phase which lies between decompensated secondary shock and irreversible shock.[15] If the animal survived for 48 hours, it was considered to have recovered from shock. Autopsies were performed on all animals.

TABLE 1.—*Physical Properties of Dextran and PVP as Compared with Water and Plasma*

	Distilled Water	Dextran	PVP	Normal Dog Plasma
Viscosity at 24.6 C., centipoise	1.0	3.35	2.26	2.50
Specific gravity	1,000	1,038	1,024	1,028
Colloidal osmotic pressure, mm. of water	0	301	402	300

RESULTS OF THE EXPERIMENTS

The viscosity, specific gravity and colloidal osmotic pressure of dextran and PVP were determined and recorded in Table 1. It is evident that the physical properties of both products closely resemble those of plasma.

RAT EXPERIMENTS

Twenty rats were given intraperitoneally 1 ml. of dextran per 20 gm. of body weight daily for nine consecutive days. The specific gravity of the blood did not undergo any changes. The mean hematocrit values before the experiment were 48 and three hours after the last injection 38. One rat died eight days after the last injection. The others were killed nine days after the last administration of dextran. There was no fluid in the abdominal cavity.

All 20 rats treated in identical manner with PVP survived. The specific gravity of the blood remained unchanged. The mean hematocrit value before

12. Hint, H. C., and Thorsen, G.: Acta chem. scand. **1**:808, 1947.

13. Porter, C. C., and Silber, R. H.: Personal communication to the authors, from the Merck Institute for Therapeutic Research, Rahway, N. J.

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15. Davis, H. A.: Shock and Allied Forms of Failure of the Circulation, New York, Grune & Stratton, 1949.

injections was 43 and after the last one 38. No fluid was found in the abdominal cavity.

The histologic examination of the liver, spleen, pancreas, kidneys, omentum, abdominal lymph nodes, and the bone marrow of five rats in each group failed to

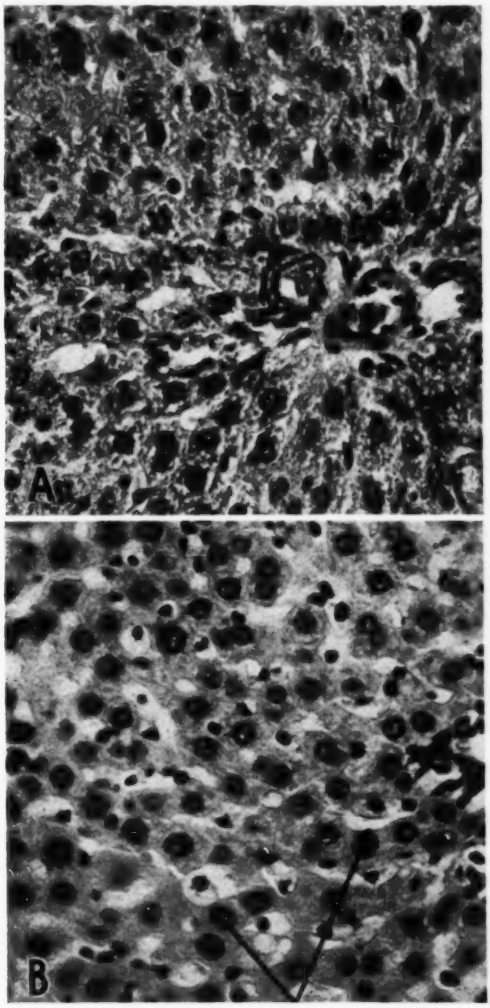


Fig. 1.—*A*, liver of a control rat. *B*, liver of a rat after nine intraperitoneal injections of PVP, 1 ml. per 20 gm.; the arrows point to two foam cells; × 400.

reveal any pathologic changes, with the following exceptions. Reticulum cells of the spleen of two PVP-treated rats contained many vacuoles, and numerous Kupffer cells in the liver of three PVP rats had foamy cytoplasm (see photomicrograph Fig. 1). In two dextran rats similar but less pronounced changes in the spleen and in the liver were noticed.

Twenty-four rats were killed at various times after a single injection of 1.5 ml. of dextran per 20 gm. of body weight, and in a corresponding group of 25 rats PVP was used to determine the rate of absorption. The data, presented in Figure 2, show that the rate of absorption was erratic. Nevertheless, after 24 hours all fluid was absorbed. The microscopic examination of the peritoneal fluid collected at various times after the injection showed few epithelial cells, white cells and red cells.

RABBIT EXPERIMENTS

Six rabbits were given 15 ml. of dextran per kilogram into the peritoneum daily. One was found dead the morning after the third injection, while the remaining five survived injections on four consecutive days. All six rabbits in the corresponding PVP series remained alive after four injections. The cumulative blood findings recorded in Table 2 indicate hemodilution. The sedimentation rate rose markedly, namely from 2.6 to 33 in the dextran series and from 2.4 to 29 in the PVP group. There were no signs of pseudoagglutination.

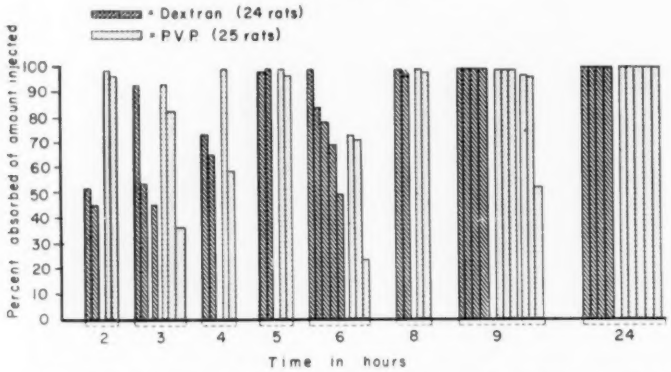


Fig. 2.—Absorption of dextran or PVP in rats after intraperitoneal injection of 1.5 ml. per 20 gm. Each column represents one experiment on one rat.

TABLE 2.—*The Average Blood Findings in Rabbits After Four Injections of Dextran or PVP, with Standard Deviations*

	Specific Gravity of the Blood	Mean Hemoglobin, Gm.	Mean Hematocrit	Mean Erythrocyte Count	Mean Sedimentation Rate	Pseudoagglutination
Control, 6 rabbits	1,051	14.3 ± 0.71%	35.3 ± 1.20%	5,330,000 ± 6.0%	3 ± 26.0%	Absent
After dextran, 5 rabbits	1,051	7.3 ± 1.36%	23.1 ± 1.16%	3,540,000 ± 3.6%	38 ± 8.4%	Absent
After PVP, 6 rabbits	1,051	9.9 ± 2.9%	27.2 ± 1.23%	4,920,000 ± 4.2%	34 ± 6.8%	Absent

Blood specimens taken from three rabbits 24 hours after a single injection of 15 ml. of macrodex per kilogram of body weight contained 4.72 mg., 4.76 mg., and 1.61 mg., respectively, of the product per milliliter of blood, thus demonstrating a considerable rate of absorption from the peritoneal cavity. Urine from a rabbit two hours after a corresponding dose of PVP contained detectable amounts of

this product. Plasma obtained from the same rabbit five hours after the injection showed distinct bluish fluorescence under ultraviolet light.

The number of rabbits used in this experiment was so small as to make statistical data concerning absorption valueless. Nevertheless it can be stated that while a large percentage of dextran was found in two instances nine hours after the last injection, no PVP could be found in the peritoneal cavity after 15 hours. The histologic examination of parenchymatous organs gave no indication of deposits of a foreign substance.

DOG EXPERIMENTS

To determine the absorption rate, 20 ml. per kilogram of body weight of dextran was injected intraperitoneally in fractional doses, after production of hemorrhagic shock in 11 dogs and the same amount of PVP in 17 dogs. The animals were killed from 4 to 96 hours after the injection, and the amount of the remaining peritoneal fluid was measured and deducted from the amount injected. The resulting data are recorded in Figure 3. The absorption rate of dextran or PVP

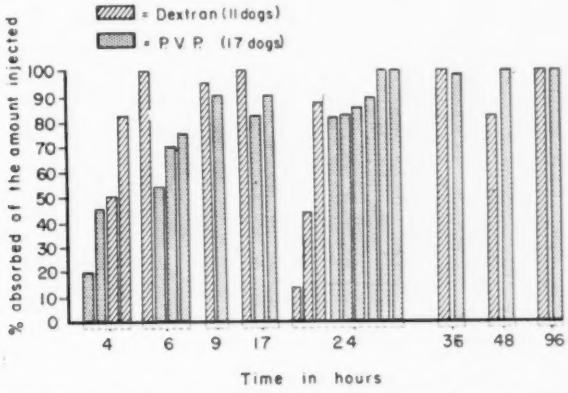


Fig. 3.—Absorption of dextran or PVP in dogs after intraperitoneal injection of 2 ml. per 100 gm. Each column represents one experiment on one dog.

TABLE 3.—*The Survival Rate of Dogs After Hemorrhagic Shock and Intraperitoneal Injection of Dextran or PVP*

	Control	Dextran	PVP
Number of dogs	50	35	35
Survived	16, or 32%	27, or 77.14%	29, or 82.85%

in control dogs was from 12 to 16% lower than in animals in which hemorrhagic shock had been produced.

Seventy dogs were bled, and after stabilization of blood pressure at the desired level the amount of dextran or PVP corresponding to the volume of blood withdrawn was injected intraperitoneally in three equally divided doses at intervals of one and a half hours. Hemorrhagic shock in 50 control dogs was not followed by any injections.

The 48-hour survival rate of 35 dextran-treated dogs was 77.14%, of 35 PVP-treated dogs 82.85% and of 50 control dogs 32.00% (Table 3).

The cumulative data showing blood changes, recorded in Table 4, demonstrate greater hemodilution and rise in sedimentation rate in the dogs which were bled than in animals which were not. A comment concerning the sedimentation rate is due. While bleeding alone, and also injections of dextran or PVP without bleeding, was followed by moderate acceleration of sedimentation rate, a considerable rise was noticed when injections were given after production of hemorrhagic shock. The cumulative effect of both factors is not sufficient to explain this phenomenon, so that a synergistic action should be considered.

Figure 4 shows that the rise of blood pressure after shock was higher in the dextran and in the PVP series than in control animals and that PVP had a stronger effect than dextran. The same statement applies to the rise in blood volume, recorded in Figure 5. The findings of Hecht and Weese [3] regarding the fall of blood pressure in the dog after PVP injection were not substantiated.

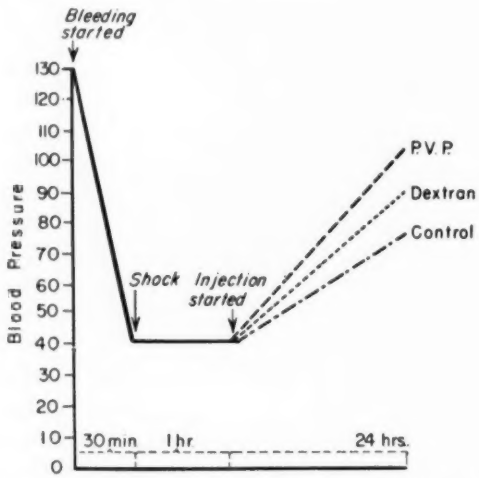


Fig. 4.—The mean blood pressure in dogs before bleeding, at the shock level and 24 hours later.

TABLE 4.—*The Average Blood Findings in Dogs Before and After Bleeding and Injections of Dextran or PVP, with Standard Deviations*

	Hemoglobin, Gm.	Hematocrit	Sedimentation Rate	Number of Erythrocytes	Pseudoagglutination
Before bleeding	15.14 ± 4.7%	42.4 ± 10.2%	13.3 ± 11.4%	6,100,000 ± 3.6%	Absent
72 hr. after bleeding and injection of dextran—35 dogs	9.6 ± 2.9%	24.4 ± 3.6%	54.3 ± 4.7%	2,990,000 ± 4.1%	Absent
72 hr. after bleeding and injection of PVP—35 dogs	6.2 ± 6.7%	21.6 ± 4.9%	71.0 ± 6.7%	2,680,000 ± 3.2%	Absent
72 hr. after bleeding, with no injection—50 dogs	10.7 ± 4.6%	26.4 ± 4.3%	18.0 ± 3.2%	3,323,000 ± 2.8%	Absent
72 hr. after dextran without bleeding—5 dogs	13.14 ± 7.1%	34.4 ± 3.4%	24.2 ± 4.1%	4,800,000 ± 4.2%	Absent
72 hr. after PVP without bleeding—5 dogs.	12.11 ± 5.3%	32.4 ± 5.4%	26.3 ± 6.3%	6,100,000 ± 4.3%	Absent

Figure 6, which depicts the results of quantitative determination of dextran or PVP in the blood, shows that considerable amounts of the agents were detectable as early as two hours and as late as five days after the injection.

PVP is known to cause a faint fluorescence when exposed to a source of ultraviolet light with a Wood filter.[16] This phenomenon could be demonstrated in serum

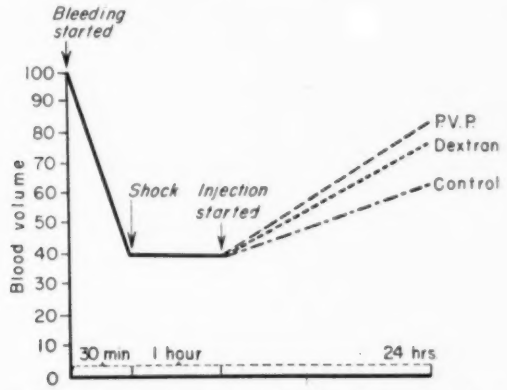


Fig. 5.—The mean blood volume in dogs before bleeding, at the shock level and 24 hours later.

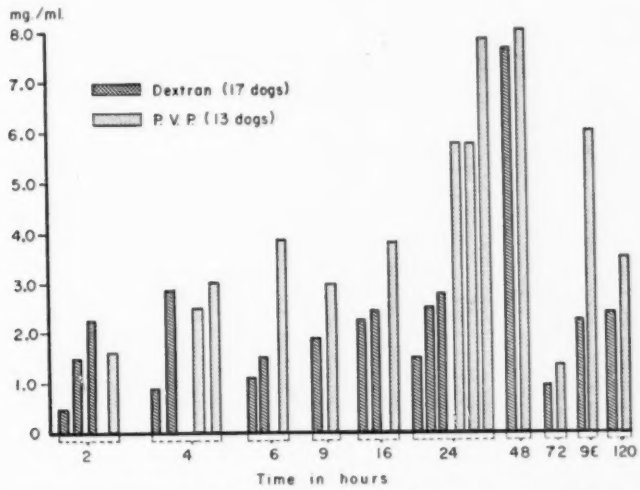


Fig. 6.—The mean dextran or PVP contents of dog's blood after intraperitoneal administration of 35 ml. per kilogram.

obtained as early as two hours after an intraperitoneal injection of PVP. The fluorescence reached its maximum six hours after the injection.

The loss of serum albumin ranged from 8 to 38% and the loss of serum globulin from 3 to 21% of the values obtained before the bleeding. A diminished albumin-

16. Benhold, H.: Deutsche. med. Wchnschr. **23**:30, 1944.

globulin ratio, as compared to the values before the bleeding, was found 72 hours later in 77% and a reversed ratio in 23% of all dogs.

The reaction to the thymol turbidity test in the blood was negative in all instances, and no blood, albumin, or sugar could be found in the urine. A careful search for foam cells in parenchymatous organs gave negative results, and there were no other detectable lesions.

COMMENTS

To evaluate intraperitoneal administration of dextran or PVP in the treatment of hemorrhagic shock, three questions must be answered: Are the products and the method innocuous? Are they therapeutically effective? What are their indications and limitations?

Repeated intraperitoneal injections of dextran or PVP were well tolerated by rats, rabbits, and dogs. No signs of local irritation or general reaction were noticed. The blood studies did not show any abnormal cells or rouleaux formations responsible for pseudoagglutination, the urine tests were negative, and the histologic examination of parenchymatous organs failed to reveal significant alterations, especially the presence of foam cells in the reticuloendothelial system, unless repeated and excessive doses were administered. It is assumed that such cells, described by several authors,[17] contain deposits of the blood volume replenishers. It was noted that although dogs exhibit a sensitivity reaction to PVP injected intravenously,[18] no such colloidoclastic reaction ever followed intraperitoneal administration of PVP. This may be due to a slower absorption rate.

The sedimentation rate was markedly accelerated, without noticeable differences between dextran and PVP. This effect is probably the consequence of the size and the shape of the molecules. The cognizance of this fact suggests the necessity of caution in interpreting the results of sedimentation studies in patients who had been given dextran or PVP.

Hypoalbuminemia was more marked than hypoglobulinemia, so that the albumin-globulin ratio was reversed in many instances. The partial elimination of the albumin fractions from the blood appears to be a part of a mechanism preventing the development of oncotic hypertension. Apparently the organism uses the foreign colloid to maintain the blood pressure and stores its own albumin. The depression or reversal of the albumin-globulin ratio was so insignificant that it did not impair the coagulability of the blood or the healing of wounds; in other words, it was of no clinical importance.

To summarize, it may be inferred from all these observations that the first question concerning the safety of the procedure, because of the dearth of untoward effects, can be answered in the affirmative.

Both plasma volume replenishers are well suited to mitigate shock as they are similar in physical properties to blood plasma, particularly in regard to viscosity and to oncotic pressure. The latter is especially important because the molecular aggre-

17. Schoen, H.: Klin. Wchnschr. **27**:463, 1949. Goldenberg, M.; Crane, R. D., and Popper, H.: Am. J. Clin. Path. **17**:939, 1947. Ammon, R., and Müller, W.: Deutsche med. Wchnschr. **74**:465, 1949. Bargman, W.: Arch. path. Anat. **314**:162, 1947. Goldenberg, M.: Am. J. Clin. Path. **17**:939, 1947.

18. Völker, R., and Barke, A.: Deutsche tierarztl. Wchnschr. **51**:261, 1943. Loubatières, A.: Compt. rend. Soc. biol. **142**:1340, 1948. Lundy, J. S.; Gray, H. K., and Craig, W. McK.: Arch. Surg. **61**:55, 1950. Hecht and Weese.[3]

gates must be large enough so that they will not readily diffuse through blood vessel walls or spill through the kidneys and small enough to (1) avoid clogging the capillaries, (2) cause sludging of the blood, and (3) produce the desired colloidal osmotic effect.

The absorption of dextran and PVP from the peritoneal cavity was demonstrated by the following criteria: (1) the amount of fluid in the abdominal cavity at various times after the injection, (2) chemical detection of the agents in the blood and the urine, (3) fluorescence of serum attributable to PVP, (4) absence of fall of specific gravity of the blood, usually following severe hemorrhage, (5) more rapid rise of the blood pressure and the blood volume following hemorrhage, as compared to controls, (6) hematologic picture which demonstrated greater hemodilution, exemplified by diminished red cell count, hematocrit and hemoglobin values than that in control animals, and (7) higher survival rates in dogs after hemorrhagic shock than in the control series.

The rate of absorption of dextran and PVP was rather erratic and unpredictable. However, the evidence indicates that in the majority of cases even relatively large amounts were absorbed within 24 hours. On the whole, dextran disappeared from the peritoneal cavity at a slower rate than PVP. The fact that the molecular weight of PVP ranges from 20,000 to 80,000, with a mean at 40,000 to 45,000, whereas dextran is hydrolyzed down to a molecular weight between 20,000 and 265,000, suggests that the high molecular portion of dextran tends to stay in the peritoneal cavity longer.

It was a priori clear that intraperitoneal drip cannot compete with venoclysis in regard to velocity of absorption. Yet the former had a resuscitating effect on dogs in shock. The high percentage of recoveries argues against the assumption that the results could be explained on the basis of change or of random sampling. Moreover, Swingle [19] reported the interesting observation that a single plasma transfusion over 30 minutes failed to prevent or even delay death in dogs after experimental shock whereas intermittent transfusions over a period of six hours had a dramatic effect. This observation tallies well with that of Guyton,[20] who found that during massive blood transfusions in dogs occurring over an average period of approximately 40 minutes, an average of 63% of the transfused whole blood and 113% of its plasma portion was lost from the circulation by the time the transfusion was completed. Price [21] pointed out that in chronic shock sudden injection of large quantities of blood results in blood wastage and that it is preferable to give numerous small transfusions at intervals. Christopher [22] states that in patients with burns it is more economical to space the injections of plasma or blood over a 36-hour period than to give most of the solution during the initial period. Lyons [23] advises multiple transfusions instead of one massive transfusion in patients with chronic shock. The conclusions may be drawn that, in opposition to the universally accepted teaching, the evanescent effect

19. Swingle, W. W., and others: Am. J. Physiol. **138**:156, 1943.

20. Guyton, A. C., and others: Am. J. Physiol. **163**:528, 1950.

21. Price, P. B.: Blood Volume in Health and Diseases, J. A. M. A. **145**:781, March 17, 1951.

22. Christopher, F.: A Textbook of Surgery, by American Authors, ed. 5, Philadelphia, W. B. Saunders Company, 1949, p. 17.

23. Lyons, C.: Penicillin Therapy of Surgical Infections in the United States Army, J. A. M. A. **123**:1007 (Dec. 18) 1943.

of a rapid transfusion may under certain circumstances be enhanced or prolonged by the employment of a method, such as intraperitoneal drip, which results in a relatively slow absorption of fluids.

The field of usefulness of intraperitoneal administration of blood volume replenishers would seem to be limited to the following indications:

1. In hemorrhagic shock. When this is present, blood transfusion is indispensable but is not always immediately available. Plasma volume replenishers may be used in such cases to tide the patient over a critical period until transfusion can be given. In such instances intraperitoneal drip as a substitute for venoclysis may be indicated, when (*a*) early evacuation makes immobilization of extremities difficult to achieve, (*b*) the magnitude of the catastrophe and the shortage of skilled personnel are such as to make a search for veins impractical, or (*c*) technical difficulties in venoclysis are encountered, for instance, collapsed, sclerotic or thrombosed veins, or obesity of the patient. However, venoclysis or intra-arterial infusion remains the first choice whenever a speedy administration of fluids is of paramount importance.

2. In imminent shock. In this condition, which is frequently observed after certain traumas, such as crush injuries of the femur, multiple fractures of the pelvis, gunshot wounds of the thorax or the abdomen, injuries of the lower cervical or the upper thoracic portion of the spinal cord, and also in many states of prostration and circulatory failure which entail a certain degree of tissue asphyxia, e. g., prolonged anesthesia, overwhelming infection, heat stroke, toxic goiter, septicemia or eclampsia, the circulating blood volume may be markedly reduced without corresponding loss of blood cells. In these cases blood volume replenishers seem well suited and the intraperitoneal route may be considered, especially when rapid introduction of fluids is not imperative.

3. In surgical patients depleted as a result of chronic infections, nutritional disturbances, or malignant disease. The term chronic shock has been applied to this syndrome, which consists of weight loss, decreased blood volume, increased volume of interstitial fluid, and intensified susceptibility to acute shock.[24]

4. In conditions characterized by escape of serum or plasma, such as mesenteric venous thrombosis, strangulation of the intestines or extensive burns, particularly when areas with easily accessible veins are affected.

5. In patients with conditions such as myocardial deficiency, in which overburdening of circulation must be avoided. If other conditions in such patients require restoration of the blood volume, intraperitoneal drip, as compared with venoclysis, offers the advantage of a slower introduction of fluids.

We wish to emphasize the fact that the number of experiments is too small and variability of certain data too great to arrive at any definite conclusions. Nevertheless, the composite picture drawn from pooled findings in rats, rabbits, and dogs justifies the opinion that judicious use of dextran or PVP in the form of intraperitoneal drip in the aforementioned conditions is of therapeutic benefit. However, the presence of foam cells in the liver and the spleen in rats suggests that excessive doses or repeated administration of dextran or PVP at frequent intervals should be avoided until more light is shed on the significance of such morphologic changes. Dextran seems to be absorbed somewhat slower and more irregularly from the

24. Clark, J. H., and others: Ann. Surg. **125**:618, 1947.

peritoneal cavity than PVP. This observation should not be construed as a proof of its inferiority when other routes of introducing this agent are employed.

The fact must be kept in mind that administration of blood volume replenishers may be able to achieve restoration of the normal volume but not of the normal composition of the blood. In other words, the main value of blood volume replenishers lies in their hemodynamic effect, which is of paramount importance in the treatment of shock.

SUMMARY

As a result of animal experiments in which dextran and polyvinylpyrrolidone (PVP) were introduced intraperitoneally the following conclusions seem justified: Both agents are absorbed well from the peritoneal cavity. Both had a resuscitating effect on dogs after production of hemorrhagic shock. While single injections of each agent failed to exhibit any deleterious effects, excessive amounts or repeated injections were found to give evidence of tissue storage.

Indications for the employment of the intraperitoneal route are discussed. On the basis of the experiments described it would seem that the method has sufficient merit to warrant further investigation.

1200 North Ashland Avenue

CARCINOID TUMORS OF THE SMALL INTESTINE

Report of an Additional Case of Malignant Ileal Argentaffinoma with Frank Mucosal Ulceration in a 32-Year-Old Woman

C. RICHARD BOWERS, M.D.
AND
J. HAROLD CHEEK, M.D.
DALLAS, TEXAS

IN THE treatment of malignant neoplasms of the small intestine, the great expectations of cure or of almost fantastic palliation routinely are found only in cases of primary argentaffine tumors. These results are obtained only through surgery, which should be as radical as the extension of the tumor demands. The excellent prognosis following such treatment of carcinoid tumors, as contrasted with the outlook in the treatment of intestinal carcinomas and sarcomas, is confirmed repeatedly in the literature. The sharp difference in life expectancy after resection of carcinoids and after resection of other malignant growths of the small bowel should never be forgotten by the surgeon, especially since carcinoids are reported to comprise one-fourth to one-fifth of the total number of malignant neoplasms of the small intestine.

This report is thus presented as a reminder to the surgeon of the surprisingly good results to be anticipated after adequate surgical treatment of small bowel carcinoids. An unusual case of a metastasizing ileal carcinoid is reported together with the treatment received and the postoperative course. A brief comment on these tumors is also presented.

REPORT OF A CASE

Mrs. P. N., a 32-year-old white woman, was admitted to Baylor University Hospital on Dec. 27, 1950, with the chief complaints of an asymptomatic, enlarging, grapefruit-sized mass in the right upper quadrant of the abdomen of two years' duration and a chronic unexplained anemia of moderately severe grade of eight years' duration.

Family History.—The only relevant finding in the family history was that the patient's father died at 52 years of age with a cancer of the colon.

Past History.—The patient sustained the usual childhood diseases without complications or sequelae. She had two bouts of bronchopneumonia as a child, also without sequelae. Over the past eight years, she had been subject to moderate anemia, the details of which are included in the description of the present illness. The past history was otherwise noncontributory.

Present Illness.—In 1943, at 24 years of age, while the patient was undergoing a routine check-up by her local physician, an anemia of moderate degree was discovered. Numerous tests and examinations were done at this time in an attempt to discover the cause of the anemia, but all these were fruitless. She was at this time totally asymptomatic. She was given monthly examinations over the subsequent few years, and because of a history of small amounts of bright red blood being passed after each bowel movement, her physician injected hemorrhoids which were present. During hospitalization, the patient was given six whole blood transfusions for her anemia, and she convalesced satisfactorily. Since that time, she has had no bleeding from the rectum, either bright red or tarry in nature. However, shortly after her discharge from

From the Department of Surgery, Baylor University Hospital.

the hospital, the anemia was found to have recurred, and it has persisted to the present time. During these eight years, the patient has received various hematogenic substances, including iron, liver, and vitamin B_{12}. Her hemoglobin has been reportedly as low as 20% at times during the past eight years.

Approximately two years ago, during one of her routine monthly examinations, her physician discovered the presence of an orange-sized, freely movable, nontender mass in the right upper quadrant of the abdomen. Being observed closely by her physician, this mass was seen to progress to the present size of a small grapefruit.. However, as far as the patient could determine, it had never produced any symptoms whatever. Because of the steady growth of the mass and the persistent refractile anemia, she was referred to the surgery service of Baylor Hospital for evaluation.

During the eight years of the present illness and the two years of the presence of the mass, the patient had experienced no pain, nausea, vomiting, hematemesis, weight loss, distention, obstipation, melena, chills and fever, jaundice or any other sign or symptom referable to the major systems. During this period, also, her menstrual cycle had been perfectly regular, with a normal flow and interval, except for a period of gestation four years previously, after which she gave birth to a normal child. The pregnancy and delivery were uncomplicated. The last menstrual period occurred on Dec. 4, 1950, and was perfectly normal, as were those preceding it.

During the past year, the patient had gained approximately 10 lb. (4.5 kg.), her weight remaining apparently constant over the preceding years.

Physical Examination.—On her admission to the hospital the temperature was 99 F. orally, pulse rate 82, and respiratory rate 18. The patient was a moderately obese, well-developed woman, not appearing either acutely or chronically ill. The mucous membranes were slightly pale. The only positive findings were confined to the abdomen and the pelvis. The abdomen was not distended, and the only asymmetry noted was a slight fulness in the right upper quadrant. On palpation, a firm, round, smooth, freely mobile, nontender mass, approximately 10 to 12 cm. in diameter, was palpated in the right upper quadrant overlying a portion of the left upper and right lower quadrants in the region of the umbilicus. This mass was freely movable in all directions, with only slight limitation of mobility in the vertical plane. During frequent subsequent examinations, it could be first found in the right lower and left upper quadrants as well as in the right upper quadrant, further demonstrating its mobile nature. There was no pain on manipulation, and the percussion note over it was flat. A smaller nodular projection of the same consistency as the larger mass was felt toward the left lower quadrant just beneath the umbilicus. The liver, spleen, and kidneys were not palpable. No tenderness was elicited anywhere in the abdomen. No external hernia could be made out. There were no abnormally prominent vascular markings over the abdomen.

Pelvic examination was noncontributory except that a few examiners believed that the cervix was displaced slightly cephalad, as the mass in the right upper quadrant of the abdomen could be dislocated in that direction. This displacement was slight, and other observers failed to elicit it at all.

Laboratory Examination.—Laboratory tests gave the following results: The hemoglobin content was 8.8 gm. per 100 cc., the red blood cell count 3,310,000, the white blood cell count 9,100, and the differential count normal. The platelets numbered 473,000, the prothrombin time was 65%, the clotting time (Lee-White), 20 min. 10 sec. and the bleeding time, 3 min. 10 sec.

Urinalysis, heparin titration, the van den Bergh test, total and fractional protein studies, and the sulfobromophthalein (bromsulphalein*) test all gave normal results. Examination of the stool consistently revealed the presence of blood (guaiac determination) ranging in amount from 2 to 4 plus, without the presence of parasites or ova. Grossly, however, the stools were of a normal dark brown color.

Routine posteroanterior and lateral roentgenograms of the chest revealed nothing abnormal. Anteroposterior and transverse roentgenograms of the abdomen revealed a somewhat homogenous mass about the size of a grapefruit over the sacrum and extending up to the lower border of the fourth lumbar vertebra. On the transverse view, this mass was seen extending upward and pushing on the abdominal wall immediately beneath the umbilicus. Barium enema revealed no evidence of an intrinsic lesion in the colon but suggested an area of extrinsic pressure from the mass on the transverse colon, cecum, and a portion of the terminal ileum.

Course in the Hospital.—After numerous investigational procedures and consultations, it was believed that the most likely possibility was that of a mesenteric cyst of long duration and venous enlargement locally, with either submucosal hemorrhage therein or ulceration explaining the persistent anemia.

On Jan. 3, 1951, celiotomy was carried out through a modified right lower transverse incision. The tumor mass, which had been felt prior to operation, was easily delivered into the wound and was found to consist of a large, rounded, smooth, firm, slightly rubbery mass measuring 12 cm. in diameter, being spherical in shape and lying between the leaves of the mesentery of the first portion of the ileum. Immediately adjacent to this was a similar but smaller mass measuring 4 cm. in diameter, and a third separate mass was found on the antimesenteric border of this portion of the ileum. The last was considered to be the primary tumor (Fig. 1). It was much more nodular and irregular in shape than the two secondary masses within the mesentery and measured approximately 5 cm. in its greatest diameter.

When this portion of the ileum was opened after the resection, an ulcer crater measuring roughly 1.5 by 3 cm. was found in the mucosa of the small bowel immediately overlying the tumor (Fig. 2). This tumor tissue was firm and had a tendency to marked eversion on cross

Fig. 1.—Resected specimen (Mrs. P. N.). Both metastatic masses in the mesentery are sectioned. Ileum, opened along the antimesenteric border, courses about metastases. Primary tumor (upper right) presents large mucosal ulcer.

section. In some areas, there were small foci of old brown punctate hemorrhage and of recent bright red ones. The tumor consisted of a glistening, granular, yellowish white, occasionally tan, spongy type of tissue which scraped from the cut surface with ease. All three portions of the tumor appeared identical on cross section.

There were no gross metastases in the mesenteric nodes except for the two secondary masses described. The liver was free of any palpable nodules, and there were no periaortic nodes found. No peritoneal implants could be identified, and there was no fluid noted in the peritoneal cavity. The only adhesions present were those wherein a small portion of the greater omentum was attached to the serosal surface of the primary nodule on the antimesenteric border of the first portion of the ileum. This portion of omentum was resected with the specimen.

The specimen included 45 to 50 cm. of ileum (with the adherent portion of omentum) and its block of mesentery resected as closely to the base as possible, including the large secondary masses. The mesentery was closed with the use of interrupted No. 60 cotton sutures on each peritoneal leaf, and an open anastomosis was done using outer simple interrupted No. 60 cotton seromuscular sutures and an inner, circumferential suture of 000 chromic catgut, four times interrupted. After this anastomosis, the lumen easily admitted one finger. The abdomen was then

closed in layers with interrupted No. 30, 60, and 100 black cotton sutures. During the procedure the patient received 1,000 cc. of whole blood and 500 cc. of 5% dextrose in distilled water, all intravenously. She had apparently withstood the procedure well and was returned to her ward in excellent condition.

Postoperatively, constant gastric suction through the Levine tube was maintained, with administration of fluids intravenously in an average amount of 3,000 cc. per day, electrolytically proportioned to the output by suction. Penicillin was given, 100,000 units every three hours intramuscularly. She also received 0.5 gm. of dihydrostreptomycin every six hours intramuscularly. Vitamins and hykinone* (menadione sodium bisulfite) were also administered. On the second postoperative day the abdomen was soft and peristalsis was in evidence; gastric suction was discontinued, and low-residue liquids were started by mouth. On January 7, a full liquid

Fig. 2.—Closer view of ulcerated primary tumor. The smaller of the mesenteric metastases lies immediately beneath the primary growth.

diet was instituted and normal bowel movements commenced after the administration of a small water and glycerin enema. The following day, a low-residue general diet was started, which was then increased on January 9 to a normal diet. The patient's convalescence was totally uneventful thereafter. The postoperative period was completely afebrile. Ambulation was instituted on the first postoperative day, and wound healing was primary and completely satisfactory.

The patient was given an additional transfusion of 500 cc. of whole blood and was discharged from the hospital on the seventh postoperative day, with a hemoglobin content of 11.5 gm. per 100 cc., totally ambulatory, afebrile, and eating and excreting well.

Pathological Examination.—Multiple sections of all three masses revealed a typical argentaffine type tumor throughout. These sections revealed the usual irregular crab-like masses of closely packed, small dense basophilic tumor cells with small amounts of azurophilic cytoplasm which was poorly defined. Peripheral pallisading was evident in these masses of cells, and

festoon formation was often present. In a few areas there was a suggestion of anaplasia as evidenced by slight to moderate variation in size, shape, and staining qualities of the nuclei. Occasional mitotic figures were also noted. Small to moderate amounts of supporting fibrous tissue stroma and focal infiltrates of inflammatory cells, chiefly lymphocytic, were also noted. In one section, a moderate-sized blood vessel was seen to contain within its lumen two groups of typical tumor cells. Del Rio Hortega stains revealed positive cytoplasmic black (argentaffine) granules in the neoplastic cells. Sections through the primary mass on the antimesenteric portion of the ileum revealed typical ileal wall being replaced in the neighborhood of the ulcer by the carcinoid, with complete absence of the mucosa. Inflammatory reaction was slightly more marked in this area. Here the tumor tissue was seen to invade all layers of ileum beneath the ulcer and extend into the peri-ileal adipose tissue. A pseudocapsular zone was seen along various borders of the three masses.

COMMENT

Carcinoids are neoplasms characterized by the tumorous proliferation of the so-called Kultschitzky or argentaffine cells of the deeper mucosa in the gastrointestinal tract and its appendages. By far the commonest site of occurrence of these tumors is the vermiform appendix. Thereafter, in decreasing order of frequency as sites of occurrence are the ileum, cecum, colon and rectum, jejunum, stomach, duodenum, gall bladder, Meckel's diverticuli and acquired jejunal diverticuli, pancreas, and mesentery. In most of the larger series of reports of primary argentaffinomas, the ratio of appendical to extra-appendical tumors varies from 2 to 1 to as high as 10 to 1, with an approximate average figure of 2.5 to 1. The over-all predilection for occurrence of these tumors in the region of the appendix and the terminal ileum is reflected in the consistent reports of the primary growths in the ileocecal region comprising 90% or more of all carcinoids of the gastrointestinal tract. It is to be mentioned that carcinoid-like tumors have also been reported in teratomas of the ovary in a few cases.

If the appendical carcinoids are excluded and only extra-appendical argentaffinomas considered, it is observed that a significant number, varying from 64 to 90%, of the extra-appendical carcinoids have their origin in the ileum, and well over half of these ileal carcinoids occur in the distal third of the ileum. The remaining carcinoids are classified as uncommon to rare and are scattered throughout the other sites in the gastrointestinal tract.

The opinion on the malignant versus the benign nature of these tumors has fluctuated over the 85 odd years that they have been observed and described. This may have been due in part to the sole consideration of appendical carcinoids in large series by some writers and the subsequent limitation of their observations to extra-appendical carcinoids by other writers.

Appendical carcinoids are largely discovered in appendixes which have been removed primarily for acute inflammatory change or in appendixes prophylactically removed during gynecologic operations. Metastasis from an appendical carcinoid has been reported only rarely, whereas extra-appendical carcinoids have a proved tendency to metastasize to lymph nodes, liver, and adjacent structures in from 28 to 40% of the cases. Series as large as a hundred or more cases of carcinoid of the appendix are reported without evidence of any metastasis whatsoever, the tumor always being confined to the appendix.

The age of the patients when appendical carcinoid is discovered is usually centered around the third decade of life, whereas patients with extra-appendical

carcinoids present themselves to either the surgeon or the pathologist in the sixth decade of life on an average.

Carcinoids of the appendix predominate in the female sex, the ratio in large groups being as high as 4 or 5 to 1 and these figures being relatively consistent in most series. Carcinoids of extra-appendical origin, however, appear to be equally divided between the sexes.

The first two differences between appendical and extra-appendical carcinoids and their subsequent courses may be explained on the basis of the anatomic differences between the appendix and the small bowel (and the remainder of the gastrointestinal tract), since even small nodules occurring in the appendix would obstruct early and produce signs of acute appendicitis, whereas the growth may extend considerably and even metastasize from the small and large bowels before any obstructive signs would occur. The third difference between appendical and extra-appendical carcinoids is rather difficult to explain unless one places some weight on the fact that probably more prophylactic appendectomies are done incidentally in women because of the large number of pelvic operations incurred by them.

About 0.5% of all gastrointestinal tumors are in the small intestine, and carcinoids constitute a fair portion of these in reported series. Ariel[1] reported an incidence of argentaffinomas of 8.3% of all small intestinal neoplasms; Dockerty and Ashburn reported that 23% of all the malignant neoplasms of the small intestine were carcinoids; St. Mary's Hospital, over a period of 18 years, reported that 14% of all small intestinal neoplasms were carcinoids, and the Long Island College Hospital reported that 33% of surgically removed primary small intestinal growths were carcinoids. The autopsy incidence of carcinoids of the small intestine varies from 0.1 to 0.22% in substantial series. From these data it would seem that the over-all incidence of small intestinal carcinoids is low and that they are frequently asymptomatic, but it must be remembered that these tumors will constitute a relatively high proportion of all growths of the small intestine causing clinical symptoms. This is especially apparent from the proportionately higher incidence of carcinoids in the neoplasms of the small intestine removed surgically than in the necropsy specimens.

HISTORY

Up until the early part of 1950, we found a total of 417 carcinoids of the small intestine recorded in the literature. Because of the widely disseminated manner in which isolated case reports and small group reports are recorded, unquestionably this figure does not include all the carcinoids which are in the printed medical literature, but it does include all the moderate-sized and larger series, as well as numerous single case reports which are in the more widely circulated literature. Suffice it to say that since the first reported case in 1867 there have been, up to 1950, over 400 of these unusual tumors reported.

Concerning the sex incidence of carcinoid of the small intestine, it has been consistently found that the proportion is almost equal, there being a slight preponderance in males. The ratio is approximately 4:3, male to female, in all the larger series. The average age incidence for carcinoid tumors of the small bowel

1. Ariel, I. M.: Argentaffin (Carcinoid) Tumors of the Small Intestine, Arch. Path. **27**:25-52 (Jan.) 1939.

reported by various authors is as follows: Cooke [2] (20 malignant tumors), 57.2 years and (68 benign tumors), 54.2 years; Dockerty and Ashburn [3] (13 malignant tumors), 58 years; Ritchie and Stafford [4] (9 tumors), 57 years; Grimes and Bell [5] (8 malignant tumors), 58 years; Ariel [1] (111 summarized cases), 57.2 years and (11 of his own cases), 56.3 years. These tumors have been reported in all decades from the third through the tenth, inclusive. The incidence in the third, fourth, and fifth decades is, however, lowest of all, reaching its peak in the sixth and seventh decades and tapering off in the eighth, ninth, and tenth decades.

CLINICAL ASPECTS

The symptomatology seen with these tumors of the small bowel may vary considerably, but a fair number of the carcinoids of the small bowel are apparently completely asymptomatic.

In the benign type of carcinoid, that is, those without any evidence of transserosal extension, intramesenteric extension, or lymphatic or blood-borne metastatic spread, clinical evidence of the lesion is lacking usually in 90% of the cases. However, in the malignant carcinoids, signs of intestinal obstruction are present usually in 50% of the cases. Of all the carcinoids of the small intestine, malignant and nonmalignant together, approximately 20 to 30% give some clinical evidence of their presence.

Sporadic mention throughout the case reports is made of palpation of an abdominal mass or masses in the presence of subsequently diagnosed carcinoids of the small bowel. These were invariably present in cases of malignant carcinoids which had metastasized, and in most cases properly evaluated these masses were found to be metastatic carcinoid tumors, since the primary tumors themselves rarely attained any palpable size. However, palpation of single or multiple masses is being mentioned more frequently in the more recent series of malignant argentaffinomas of the small bowel.

Melena is considered by most authors as an unusual sign of argentaffinoma of the small bowel, since most observers feel that ulceration of the mucosa by carcinoid is the exception rather than the rule. Unexplained anemia, cachexia, and weight loss are also mentioned as single or combined complaints in a small percentage of the cases.

Unquestionably, recurrent partial intestinal obstruction with bouts of distention, cramping abdominal pain, anorexia, or nausea or vomiting, with or without intermittent diarrhea, constipation, and numerous dyspeptic complaints, constitute the common symptomatology of the clinically manifest carcinoids of the small bowel. The chronicity and the recurrent tendencies of this partial obstruction are also to be kept in mind as fundamental in this disease. Cases are reported in which

2. Cooke, H. H.: Carcinoid Tumors of the Small Intestine, Arch. Surg. **22**:568-597 (April) 1931.

3. Dockerty, M. B., and Ashburn, F. S.: Carcinoid Tumors (So-Called) of the Ileum: Report of Thirteen Cases in Which There Was Metastasis, Arch. Surg. **47**:221-246 (Sept.) 1943.

4. Ritchie, G., and Stafford, W. T.: Argentaffin Tumors of the Gastrointestinal Tract, Arch. Path. **38**:123-127 (Sept.) 1944.

5. Grimes, O. F., and Bell, H. G.: Carcinoid Tumors of the Intestine, Surg., Gynec. & Obst. **88**:317-325, 1949.

these symptoms have been present and apparently attributed to the tumor itself for 20 years or more. This is readily explained by virtue of the slow growth of the tumors, as has been confirmed in numerous instances by postsurgical observations and, later, necropsy confirmation.

Of help in the differential diagnosis might be the roentgen sign of Miller and Herrmann,[6] which consists of the finding of a small intraluminal tumor together with coincident kinking of the bowel. These findings are demonstrated at the point of obstruction when a contrast medium is employed. When so observed, they are reportedly pathognomonic of malignant argentaffinomas of the small intestine.

PATHOLOGY OF CARCINOID TUMORS

Benign argentaffinomas exist almost universally as submucosal, freely movable, small nodules averaging usually less than 1 cm. in diameter and being soft to firm in consistency. Cross section reveals the tumors to be grossly encapsulated, to have a slight tendency to evert, although this is not at all constant, and to have a definite yellowish hue. Some observers described this color as ranging from a brilliant orange to a pale yellow. Close scrutiny of the gross specimen will frequently reveal the fine interlacing network of white, fibrous, almost gelatinoid bands, with clusters of yellowish, almost spongy-like tissue interspersed among this lattice work. The tumors are almost invariably homogeneous and show little tendency, if any, toward necrosis or liquefaction. No record of calcification in any argentaffinomas of the small bowel could be found. As a rule, these smaller benign argentaffinomas rarely ulcerate the mucosa grossly. Dockerty and Ashburn, as well as others, have reported occasional microscopic or small macroscopic superficial mucosal ulcerations overlying the tumors, but most observers persist in defending their nonulcerating propensity. These lesions may occasionally project partially within the lumen of the bowel, but as a rule they tend to remain sessile and only infrequently become pedunculated in a polypoid fashion.

The malignant argentaffinomas show similar gross characteristics on cross section, except that there may be an occasional area of necrosis or liquefaction which is small. Usually, the metastatic deposits seem to have more of a tendency to evert on cross section. These malignant carcinoids show definite tendencies to transgress the muscular as well as the serosal coats and produce a marked puckering and umbilication, especially in the serosal and mesenteric areas. The mesentery and the fat between the mesenteric leafs are frequently invaded and retracted into this umbilicated mass. It is at this point that kinking of the bowel itself may be seen over such umbilicated and retracted mesentery. Adjacent mesenteric and serosal seeding of the tumor is occasionally seen. Tumefactive mesenteric and deeper retroperitoneal lymph nodes are often seen in the malignant argentaffinomas, frequently measuring many centimeters in diameter. Actually, in the malignant argentaffinomas, the usual finding is a primary lesion in the small intestine which is substantially smaller than the metastatic and secondary deposits. Cross sections through the metastatic portions of the tumor are identical grossly with those of the primary tumor. The malignant argentaffinoma seems to show more of a tendency toward ulceration since there is invasion and fibrous retraction of the adjacent

6. Miller, E. R., and Herrmann, W. W.: Argentaffine Tumors of the Small Bowel: A Roentgen Sign of Malignant Change, Radiology **39**:214-220, 1942.

mucosa overlying the tumor and occasionally in a substantial portion of the circumference of the bowel, although as a rule these tumors are not annular. A few definite annular constricting carcinoids of the small intestines are on record.

Metastases from malignant carcinoids are commonest in the mesenteric and other regional lymph nodes. Liver and serosa of bowel, as well as omentum and distant nodes, are next involved in that order of frequency. Metastases have been reported in several cases to bone, spleen, and the peritoneal recesses. An occasional metastasis has been reported in the myocardium of the heart, pancreas, spleen, kidneys, adrenals, and ovaries. Metastases have also been reported in the vaginal vault, testicle, dura mater of the spinal cord, and lung. It is to be understood that in the locally invasive malignant argentaffinomas, the lymphatic vessels, blood vessels, and nerves are also frequently invaded.

The tumor cells themselves are fairly consistent and as a rule do not show much variation. The cell is small and epithelium-like, with an oval or round nucleus having a sharp nuclear membrane and finely granular chromatin. The cytologic architecture is consistently the same as that described in the sections of the tumor in the above case report. That these tumors are derived from the argentaffine cells, or the Kultschitzky cells of the crypts of Lieberkühn, is universally accepted today. However, there is still much debate as to the true origin of these argentaffine cells, whether it be mesodermal, entodermal, neuroectodermal, or from some heterotopic tissue.

It is the general concensus of most of the pathologists that there are no reliable cytological criteria for differentiation between clinically benign and metastasizing carcinoid tumors. Microscopic invasion of vessels and nerves, as well as transgression of the muscular coats, is frequently in evidence in appendical carcinoids in which metastases are rarely seen. Apparently, the gross evidence of extension into mesentery, serosa, and nodes and the setting-up of secondary metastases are the only reliable criteria for differentiation between benign and metastasizing carcinoids of the small intestine.

It is interesting to note that as more and more carcinoids of the small intestines are being reported the incidence of concurrent metastases from these carcinoids appears to be increasing statistically. This is probably due to the fact that carcinoids of clinical importance are being reported in preponderance now, whereas the earlier reports included small carcinoids found incidentally at necropsy and at operation. Of the present group of 417 carcinoids of the small bowel which we have totaled, 166 have metastasized, which is a malignancy index of 39.8% and a figure being more nearly approximated in all the current series of these tumors reported.

TREATMENT

All observers agree on the slow-growing nature of this type of tumor, regardless of the site of origin or the age of the patient. The optimum treatment of these tumors proved again and again in the literature is a radical and complete resection of the tumor with any areas of metastases which may be present. When this type of surgery can be done, the results in the majority of cases might be termed as curative.

In widely metastatic carcinoids, one removes the primary tumor and produces local palliation by the eradication of the potential obstruction in this area. Such a

procedure is likewise of paramount importance, since it has been shown that in primary resections, or even simple biopsy procedures, known metastases may often remain unchanged or even regress as long as 20 years postoperatively, the patients gaining weight and returning to normal clinically.

In summary, it might be reiterated that drastic surgery directed against carcinoid tumors of the small bowel will produce excellent results and that certainly an attitude must be adapted toward this tumor which is basically different from the attitude held toward other malignant growths of the intestine. It is to be remembered that if all the visible tumor is resected at a first or second-stage operation the chances are excellent that there will be a definite cure, and if all the tumor cannot be removed because of widespread dissemination, palliation beyond all expectations, as based on the treatment of other malignant neoplasms of the small bowel, will be obtained in a substantial percentage of cases if only some physiological continuity of the gastrointestinal tract can be reestablished, even in the presence of the tumor. To date, x-ray therapy is of no proved value in the treatment of carcinoid or its metastases, although there is totally insufficient evidence in the literature in regard to this point.

SUMMARY

A case of an unusual metastasizing carcinoid tumor of the ileum is presented in which the primary tumor ulcerated the ileal mucosa in an area 1.5 by 3 cm., probably one of the largest carcinoid ulcers in the small bowel reported. Another unusual feature is that the presenting signs in this patient were unexplained anemia (chronic blood loss type) and an asymptomatic abdominal mass of two years' duration; intestinal obstruction was never present. The patient was 32 years old, unusually young for such a tumor. The more usual feature was that the palpable masses were found to be the metastases, which were many times larger than the primary tumor. A block resection of the primary tumor and the metastases is believed curative.

The incidence, clinical aspects, diagnosis, pathology, treatment, and prognosis of carcinoid tumors of the small intestine are mentioned briefly.

Four hundred and seventeen carcinoids of the small bowel have been collected, of which 166 had extended, spread or metastasized, an over-all malignancy index of 39.8%.

The amazingly good results following surgical extirpation of these tumors and metastases (when present), or even following strictly palliative procedures (especially exclusion or bypass enteroanastomosis) when removal is utterly impossible, warrant constant attempts on the part of the abdominal surgeon to segregate these unusual tumors correctly and radically attack them.

ADDENDUM

T. J., a 49-year-old Negro, was admitted on our service two weeks ago with a history of recurrent attacks of lower and mid-abdominal cramping pains associated with moderate distention of the abdomen and nausea, but no vomiting. His first such attack occurred six years previously, and he was subject to them only infrequently up to six months ago. There was obstipation during these attacks, which lasted from 2 to 10 days. They subsided spontaneously, with the patient reverting to normal between them except for the presence of mild anorexia. The patient

had noted no blood of any kind in his stools. He had lost 35 lb. (15.9 kg.) of weight in the past six months, during which time the attacks had become more frequent. Physical examination revealed a fairly emaciated man in some discomfort from intermittent cramping abdominal pain. During the cramping pains, loud borborygmi were audible. There was mild general abdominal distention, and tympany was elicted over the entire abdomen. A hard, orange-sized mass was felt in the right paraumbilical region. This mass moved fairly well with respirations but was not mobile in the horizontal plane. No other masses or organs were felt. Laboratory studies revealed a hemoglobin content of 11 gm. and a prothrombin time of 50%. Other laboratory data were normal. All roentgenograms were normal, except for the flat plate of the abdomen, which showed a moderate distention of a few loops of small bowel in a pattern of mechanical obstruction. A barium enema was unsuccessful because of lack of cooperation by the patient. The differential diagnosis included carcinoid, or other type of small bowel tumor, possibly benign, versus a cecal carcinoma. Intermittent small bowel intussusception was believed to explain recurrent episodes of obstruction. After Cantor tube decompression and preparation of the colon with succinylsulfathiazole (sulfasuxidine®) and terramycin, the abdomen was explored through a right mid-transverse incision. A carcinoid tumor was found forming a mass in the ileocecal region, with moderately dilated and hypertrophied ileum. The terminal few centimeters of the ileum were telescoped within the cecum. The mesoileum and adjacent cecal wall consisted of a nodular tumor mass, which umbilicated and retracted the serosa everywhere. A few plaque-like implants were identified on the serosal surfaces of the jejunum and in the parietal peritoneum of the cul-de-sac. A radical right ileocolectomy was done, in which the retroperitoneal tumor masses had to be stripped off the main trunk of the superior mesenteric artery and vein. Superiorly, the adventitia and part of the muscular coat of the inferior surface of the third portion of the duodenum were denuded, in order to remove all of the tumor in this area. Similarly, the adventitia of the anterior middle third of the right ureter was denuded. An end-to-end ileotransverse colostomy was done in the closed one-layer method. In this manner all the primary tumor with its visible secondary deposits was removed, excepting the serosal implants.

The patient is now convalescing uneventfully. In this case, the primary tumor and its secondary nodal deposits, as well as its intramesenteric deposits, were removed en bloc. Several small serosal implants were left behind. We believe, however, that this man can now expect many years of symptom-free life, owing to the well-known tendencies of this type of tumor to progress very slowly.

The routine microscopic sections showed a typical carcinoid tumor arising in the ileum 2 in. (5 cm.) proximal to the ileocecal valve, with numerous regional lymph node and intramesenteric metastases. The primary tumor in the ileum measured 2 by 3 cm. and was covered by a thin mucosa. This nonulcerated primary tumor had a broad base and appeared slightly polypoid. There were numerous submucosal metastases in the adjacent few centimeters of ileum. Del Rio Hortega stains revealed argentaffine granules within the cytoplasm of the tumor cells.

SOME LIMITATIONS OF LUMBAR SYMPATHECTOMY IN ARTERIOSCLEROSIS OBLITERANS

Early Results in One Hundred Consecutive Cases

R. GLENN SMITH, M.D.

MILES GULLICKSON, M.D.

ROCKFORD, ILL.

AND

DARRELL A. CAMPBELL, M.D.

ANN ARBOR, MICH.

GENERALLY favorable comments have recently been made concerning the use of lumbar sympathectomy in the treatment of arteriosclerosis obliterans. Improvement following this procedure has been thought to be (1) dependent on elimination of the vasospastic factor; (2) an increase in collateral circulation, and, perhaps, (3) a decrease in response to certain detrimental environmental factors such as exposure to cold. The degree and duration of the benefits which may be expected from lumbar sympathectomy in arteriosclerosis obliterans and reliable criteria for the selection of cases have not yet been fully determined. Although many surgeons suggest that little is to be lost, even in severe cases, a too enthusiastic attitude may, in time, bring discredit on a procedure which will certainly salvage many properly selected extremities. For this reason, the following represents an analysis of 100 consecutive lumbar sympathectomies for severe arteriosclerosis in an effort to determine which patients, if any, have derived no benefit from the procedure.

Sympathectomy has been employed in the treatment of the late complications of arteriosclerosis, such as gangrene, ulceration, and disabling subjective symptoms, as well as in the prophylaxis of these unfortunate sequelae. We have become optimistic over the advantages of this operation in the earlier cases, but in this survey of our first 100 cases we were unable to contribute confirmatory evidence of similar advantages in the more advanced cases. Only six patients in this group were operated on solely for prophylactic reasons, and although all have responded well, the number is not large enough to permit definite conclusions. The remaining 94 extremities being reported on here were treated because of advanced complications. The results indicate some instances in which sympathectomy cannot be expected to benefit the patient in sufficient degree to warrant its use.

PREOPERATIVE DATA

The right leg was involved in 53 and the left leg in 47 instances among the first 100 arteriosclerotic lower extremities for which lumbar sympathectomies were performed. No simultaneous bilateral sympathectomies were performed, but in 17

From the Department of Surgery, Wayne County General Hospital, Eloise, Mich.

patients both sides were eventually operated on, and thus only 83 patients are represented.

The ages of the patients varied from 42 to 82 years, with an average of 62.3. This procedure would be infrequently applied if age limits as indicated by some are imposed.[1] The current methods for preoperative evaluation of candidates for sympathectomy indicate that selection of an arbitrary age limit is neither desirable nor feasible. Because of the nature of the disease, patients do not present themselves for therapy until they are of advanced age.

There were 19 women, 15 of whom had diabetes, and 64 men, 13 of whom had diabetes. In all patients the diabetes was readily controlled, and the diabetic patients are not separately discussed.

The clinical findings varied considerably, and in some patients more than one of the conditions enumerated in Table 1 were present. There were 31 extremities with intermittent claudication, 54 with variable degrees of resting pain, 42 with coldness, 27 with gangrene, 41 with ulceration, 20 with atrophy, and 32 with edema. The recorded examinations of 81 of the extremities noted absence of a palpable dorsalis pedis arterial pulsation in 65 (80%), of a posterior tibial arterial pulsation in 64 (79%), of popliteal pulsation in 26 (32%), and of femoral pulsation in 5 (6%). The absence of palpable pulsation is not always indicative of obstruction of the underlying vessel, and different examiners frequently do not offer identical opinions.

Demonstration of an increase in skin temperature of the extremity following sympathetic block has usually been considered to indicate that a favorable result could be expected from sympathectomy. Of our patients, 57% exhibited such an increase. The 100 cases which we are reporting were unselected in that patients were excluded from consideration for sympathectomy only if salvage of the extremity was impossible because of already inadequate viable tissue for good function or if the general condition of the patient prohibited surgery.

Forty-five of these patients were subjected to arteriographic examination of the vascular system. The patients were grouped according to a previously described classification.[2]

A transverse skin incision with an extraperitoneal muscle-splitting approach was used in all cases. The second and third lumbar ganglia, and in some instances the fourth, were removed.

Three patients died after operation, two of pneumonia, and one as a result of thrombosis of the abdominal aorta. In the latter, an aortogram was performed under direct vision after completion of the sympathectomy. Overzealous attempts to stanch a resultant bleeding point apparently caused dislodgement of a calcified plaque. A postoperative partial paraplegia occurred, followed by gangrene in the extremities, necessitating amputation of one. Death occurred two months after sympathectomy. The possibility of dislodging a calcified plaque during manipulation of the aorta has recently been emphasized by Pratt.[3]

1. Lowenberg, E. L.: Modern Management of Peripheral Vascular Disease, South. Surgeon **13**:187-203, 1947.

2. Campbell, D. A., and Smith, R. G.: Arteriography in the Evaluation of Arteriosclerotic Disease of the Lower Extremity, Am. J. Surg. **80**:76-79, 1950.

3. Pratt, G. H.: Peripheral Arterial Disease: Recent Advances in Surgical Treatment, J. Michigan M. Soc. **48**:1477-1483, 1949.

RESULTS OF THERAPY

I. *Major Subjective Symptoms.*—In most of the sympathectomized extremities an increase in skin temperature and temporary relief of pain and intermittent claudication occurred. In many patients, however, this relief lasted only a few days. In the final analysis we concluded that there was significant lasting relief or improvement of intermittent claudication in 10 extremities of 31 (32%) and of pain in 21 of 54 (39%). Although only 42 patients complained of coldness of the extremity before operation, 46 stated that the leg felt definitely warmer after operation.

II. *Ulceration.*—In many extremities with ulceration there was superficial gangrene of the skin edges of the ulcer. In this study such extremities were not classified as having gangrene, unless there was also frank gangrene of the digits or other areas of the foot or leg involving deeper tissues. As may be seen in Table 2, 9 extremities (33%) of those with ulceration and no gangrene were healed. Another

TABLE 1.—*Response of Major Symptoms to Lumbar Sympathectomy*

	Number	Healed or Improved	Amputated
Intermittent claudication	31	10	..
Pain	54	21	..
Coldness	42	46	..
Gangrene	27	6	17
Ulceration	41	18	19

TABLE 2.—*Influence of Lumbar Sympathectomy on Extremities with Ulceration and No Gangrene*

	Number	Healed	Improved	Toe Amputated	Leg Amputated
Toe	7	1	0	4	2
Foot	8	3	2	1	0
Leg	12	5	3	0	1

5 (19%) were improved but not entirely healed. In 5 (19%) it was necessary to amputate at least one toe. In 3 (11%) it was necessary to perform major amputation of the extremity because of subsequent development of gangrene.

III. *Gangrene.*—In our series the results of sympathectomy in patients with fully developed gangrene are not encouraging. There was a salvage rate of 39% in these patients, which is considerably lower than the 70% salvage rate attained by Coller and his associates.[4] Our results are more in agreement with those of Telford and Simmons,[5] who report a salvage of 21 extremities of 41 with gangrene (50%).

Results in the group classified according to the extent of arterial involvement indicate the considerable influence of the extent of arterial occlusion on the salvage rate. All extremities with gangrene in which there was occlusion of the popliteal

4. Coller, F. A.; Campbell, K. N.; Harris, B. M., and Berry, R. E. L.: The Early Results of Sympathectomy in Far Advanced Arteriosclerotic Peripheral Vascular Disease, Surgery **26**:30-40, 1949.

5. Telford, E. D., and Simmons, H. T.: Sympathectomy in Peripheral Arteriosclerosis, Brit. M. J. **1**:386-387, 1946.

or femoral arteries subsequently were amputated, whereas there was a salvage rate of 75% in those extremities with gangrene which had at least one patent major artery below the knee.

It has been a previously expressed opinion that those extremities with high occlusion of the femoral artery responded well to sympathectomy.[5] We found this to be true in 17 cases of obstruction of the femoral or popliteal artery without gangrene. Only two of these eventually were amputated (88% salvage rate). The explanation for the vastly different results in cases with and in those without gangrene but with the same degree of major arterial obstruction lies in the presence or absence of an adequate system of collateral vessels. Those with gangrene represent not only a failure of the main arterial circulation but a failure of the collateral circulation as well. We feel that emphasis should be placed on the recognition of patients who have, by good fortune, an adequate system of collaterals. Just as some persons are short and others tall, so do some patients have collateral vessels which, when put to the test, are large enough to sustain an entire extremity at a viable level. By a release of vasomotor tonus, such extremities can be salvaged for an indefinite period. Arteriography is of great assistance in the selection of these patients.

TABLE 3.—*Influence of Sympathectomy on Extremities with Gangrene*

Location of Gangrene	Number	Amputations		
		Toes Only	Toes, Then Leg	Leg
One toe only	14	5	6	2
Two or more toes	10	3	3	3
Foot	2	0	0	2
Leg	1	0	0	1

IV. *Response in Patients with a Decrease in Skin Temperature Following Sympathetic Block.*—There is some doubt as to the clinical significance of a decrease in skin temperature after sympathetic block. Such a decrease occurred in three of our cases. In one, the finding was proved to be erroneous by the rise in skin temperature which followed sympathectomy. The other two extremities were amputated. These cases clearly do not justify a conclusion. However, the observations of others in this respect appear sufficient to suggest that one should proceed with great caution if procaine block of the lumbar sympathetic vessels produces a decrease rather than an increase in skin temperature.

V. *Response in Patients with a Severe "Ischemic Syndrome."*—Six cases presented a syndrome characterized by major arterial occlusion, marked edema of the extremity, constant severe resting pain aggravated by elevated or horizontal position of the extremity, and, in most instances, a history of intermittent claudication prior to the onset of intractable pain. In all these cases a variable degree of decrease in the pain and edema occurred after sympathectomy, but the apparent benefit was only of a few days' duration. In every patient severe pain recurred and progressive gangrene necessitated amputation of the extremity within several weeks or months.

COMMENT

Many of the patients in this series were benefited by sympathectomy. However, of the 100 patients, 6 were asymptomatic to begin with, 25 subsequently lost an

extremity, and 3 died postoperatively, leaving only 66 whom we may examine for early evidence of beneficial results. A careful check of the records of these 66 cases indicates that in 45 extremities there were encouraging early therapeutic results, i. e., healing of ulceration, relief of pain or intermittent claudication, or salvage of an extremity with early gangrene. This figure represents 48% of the 94 patients who underwent sympathectomy for other than prophylactic reasons.

In the remaining 21 cases there may have been occasional instances in which sympathectomy aided in preventing further loss of tissue, although conservative surgical procedures alone and therapy other than sympathectomy are often successful in the control of minor areas of gangrene or ulceration in arteriosclerosis.

It is too early to be certain whether the incidence of amputation in these 66 extremities in the future will be less than that in a comparable group not subjected to sympathectomy.

In a separate study on the postoperative progress of patients who have undergone amputation of a lower extremity we have noted a lower mortality, a lower morbidity, and a higher incidence of primary healing in those patients who have previously undergone sympathectomy. We are not of the opinion that this alone is sufficient reason to subject these patients to sympathectomy.

As previously stated, we are impressed with the probable prophylactic value of sympathectomy in arteriosclerosis without gangrene. In view of the poor response to lumbar sympathectomy for those extremities which already have frank gangrene and of the high incidence of eventual bilateral amputations, it would appear a wise course to perform sympathectomy on the good leg in a patient with a gangrenous process in the contralateral foot. Maintaining the integrity of a remaining leg would seem more important than making gestures toward the treatment of a foot whose ability to survive has in many instances already been decided.

We utilize sympathectomy in all cases of arteriosclerosis in which there is demonstrable evidence of impaired circulation in the femoral trunk or one of its major branches except those falling into the categories described in the following conclusions.

CONCLUSIONS

There are three categories of patients for whom sympathectomy holds little or no promise of saving the extremity. These are (1) patients with gangrene in whom the arteriographic or clinical examination reveals occlusion of the popliteal or femoral arteries, (2) patients who have an arteriosclerotic syndrome of a lower extremity characterized by a history of intermittent claudication, marked edema, arterial occlusion, and severe resting pain aggravated by an elevated or horizontal position of the extremity, and (3) patients who have an actual drop in skin temperature of the extremity after lumbar sympathetic block.

CERVICAL TRACTION FRAME

E. F. SCHMERL, M.D.
OAKLAND, CALIF.

CERVICAL traction, alone or in combination with postural training, exercise, and massage, is a recognized form of physical therapy.[1] This article is to introduce the cervical traction frame, a device which will permit neck traction to be applied while the patient is ambulant. It is designed for cases in which repeated and continual cervical traction is indicated. It consists of a simple frame (Fig. 1) from which an ordinary head halter, strapped to chin and occiput, is suspended. The frame is small enough to rest on both shoulders by means of rounded shoulder pads with a sponge rubber base. Firmly attached to these is a "boot" which receives the frame itself. The opening in which the frame rests is cone-shaped and has an oval base permitting the shoulders a reasonable degree of movement.

The chief advantage of such a frame is obvious: Traction can now be applied during activities like housework or play. The patient is not confined to a certain place and to a certain position during traction; he does not have to stay in bed or sit under a doorframe. He also can apply the apparatus whenever pain demands it, and the physician has more freedom in regulating frequency as well as length of treatments. When prolonged continuous traction is required, this frame will not replace bed traction or the Thomas collar until further clinical experience has been gathered. It is rather another addition to our armamentarium.

In contrast to the Thomas collar, which, on account of its rigidity, is often not well tolerated in certain cases in which traction is desirable, this frame assures some motility. The active patient while in traction will take advantage of the absence of muscular spasm and will unconsciously exercise the neck.

In this age of psychosomatic medicine it does not seem to be venturing too far to consider the psychological effects of therapeutic measures. It may be claimed that neck traction by stationary suspension is somewhat undignified, depressing, and, at times, neglected and even refused by the patient. Perhaps it produces a state of mind which is not conducive to overcoming tension and postural weakness. If this aspect of the problem has any foundation at all, the ambulatory frame traction would be not only more acceptable but also, for psychological reasons, more helpful to the patient.

The amount of traction can be controlled by lengthening or shortening the upper strap. It can be easily changed during traction by the patient himself. The head can be moved about to an extent which is equal to that obtained with conventional ways of traction. Rotation of the head is facilitated by means of sliding side brackets (*br*. Fig. 2) which have a curved horizontal slit. These brackets pull the halter in

1. Haggart, G. E.: Value of Conservative Management in Cervicobrachial Pain, J. A. M. A. **137**:509 (June 5) 1948.

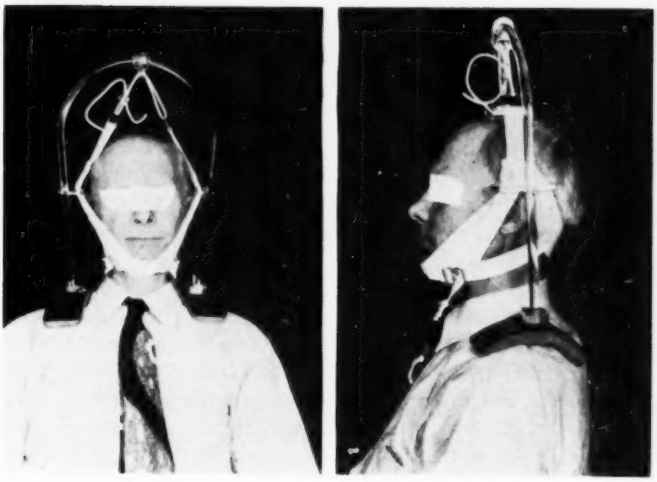


Fig. 1.—Cervical traction frame in position.

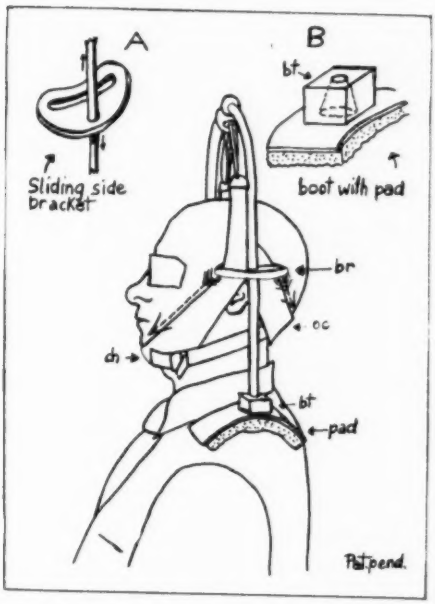


Fig. 2.—Dotted arrows indicate bracing effect of the sling by which the frame is kept in position. *A*, sliding side bracket with slit for sling strap. *B*, boot with shoulder pad showing cone-shaped boot opening for frame leg

a lateral direction and thus reduce the discomfort which a sling sometimes causes at the mandible and at the cheeks. Moreover, this pressure can be shifted or relieved by occasionally adjusting the brackets up or down.

The weight which rests on the shoulder is roughly the sum of the weight of the frame plus the amount of traction. The whole frame, which is slightly elastic, weighs only 400 gm. It is believed that when traction is prolonged less pull is required for comparable relief. Actually, this relief of pain is probably a better measuring stick than pounds of weight, which are either applied arbitrarily or are determined by the resulting relief. The comfort of the patient was found to be the best guide.

The casual observer may fear that the frame will slide off easily or tip forward or backward. Figure 2 shows how the frame is planted securely on the shoulders and held in place above the head. It is impossible for the frame to spread its "legs" because they are held together at the slit brackets by the halter straps. Tipping is forestalled by the action of the occipital cradle (*oc*), which prevents a forward tilt, and of the chin cradle (*ch*), which prevents a backward tilt. The frame will follow the head movements, and this will hardly lead to a displacement. Since the boots (*bt*) have, as described above, the cone-shaped openings, a great deal of freedom is provided for shoulder movements.

SUMMARY

A frame is described to be used in cervical traction. It permits the patient to be ambulant and active during traction. Obviously, treatments with the use of such a frame are more convenient to the patient and can be more frequent, of longer duration, and better timed than when stationary suspension is employed.

CRITIQUE OF MUSHROOM-CATHETER TREATMENT OF ACUTE GASTRODUODENAL PERFORATION

GIFFORD V. ECKHOUT, M.D.
DENVER

THE FIRST successful operation for a perforated peptic ulcer was credited to Heussner and Roux in 1892 by Brunner,[1] who collected the first large series of perforations in 1903, reporting a mortality of 48% in 387 cases. Alfred Neumann,[2] in 1909, reported the first series of perforated ulcers treated by the insertion of a catheter into the perforation providing exterior drainage of the bowel. In 1913 his series included 13 patients, with a mortality rate of 48%.[3] In the same paper, he reported a mortality of 60% with the method of closure of the perforation by suture. He described the catheter method as being useful in perforations with so much induration and friability as to make closure impossible. Turner [4] in 1925 reported on 28 patients treated by the same method. The Neumann catheter method was not generally employed during the next two decades. However, the technic has been oftener employed in recent years.[5] The method has the advantage that it does away with the indwelling nasogastric tube for constant suction in the postoperative period, thus adding to the comfort of the patient.

It is the purpose of this paper to compare the efficacy of the mushroom-catheter method with the more generally used technic of closure of the perforation reinforced with omentum.

METHOD

The records of patients who had acute gastroduodenal perforations were obtained for the period 1944 through 1950 from four general hospitals. Three of

From the Department of Surgery, University of Colorado School of Medicine. This study was the basis of a thesis presented as partial fulfillment of the requirements for the degree of Master of Science in Surgery.

1. Brunner, F.: Das acut in die freie Bauchhohle perforierende Magen- und Duodenalgeschwur, Deutsche Ztschr. Chir. **69**:101-235 (July) 1903.

2. Neumann, A.: Zur Verwertung der Netzplastik bei der Behandlung des perforierten Magen- und Duodenalgeschwurs, Deutsche Ztschr. Chir. **100**:298-305 (Dec.) 1909.

3. Neumann, A.: Perforated Peptic Ulcer, Deutsche med. Wchnschr. **39**:554-556 (March) 1913.

4. Turner, G. G.: Perforation of Gastric and Duodenal Ulcers and After, Lancet **1**:183-185 (Jan. 19) 1925.

5. (*a*) Anderson, R. H.; Allen, G. L., and Packard, G. B.: Factors Influencing the Prognosis in Acute Perforated Peptic Ulcer Based on a Review of 59 Consecutive Cases at the Colorado General Hospital, Rocky Mountain M. J. **42**:661-665 (Sept.) 1945. (*b*) Karpati, O.: Causes of Acute Perforated Peptic Ulcers, Gyógyászat. **70**:505-508 (June 15) 1930. (*c*) McCabe, E. J., and Mersheimer, W. L.: Acute Gastro-Duodenal Perforations, Am. J. Surg. **62**:39-49 (Oct.) 1943. (*d*) Nicolas, L.: Surgery of the Perforated Gastro-Duodenal Ulcer, Arch. Klin. Chir. **191**:602-605 (Feb.) 1938. (*e*) Packard, G. B.: Personal communication to the author.

the four hospitals were private institutions, and one was a university charity hospital. The cases were divided into groups according to the method of treatment, and each group was studied on the basis of the duration of the perforation before the institution of treatment, the size of the perforation, the average age of the patients, the development of complications, the average hospital stay, the mortality rates, and the follow-up results. A critical analysis was made of those cases in which death occurred to determine, if possible, whether the cause of death could be related to the method of treatment.

The mushroom-catheter technic for the treatment of acute gastroduodenal perforations is as follows. An upper right rectus incision is used. If the perforation is larger than the size of a No. 16 mushroom catheter, the use of the catheter is contraindicated.[5e] If the perforation is smaller, a mushroom catheter approximately the same diameter as the opening is placed into the bowel through the perforation so that the flange of the catheter lies snugly against the mucosa. The wall of the perforation is more tightly secured about the catheter with interrupted sutures or a purse-string suture to prevent any leakage from occurring around the catheter. The catheter is then threaded through a portion of live omentum. This omentum is sutured to the bowel around the catheter as an added precaution against any leakage. The catheter is then led out through a stab wound in the right flank and the abdominal wound closed either with or without further drainage. It is not necessary to use a nasogastric tube in the postoperative period unless the patient vomits. Suction is attached to the mushroom catheter, which prevents vomiting in the majority of cases.

When active peristalsis begins, the catheter is clamped for alternating periods and the patient given a graduated diet. When he is able to consume sufficient nourishment by mouth with the catheter clamped without causing vomiting, the catheter is removed in the same manner as that employed for removing a T-tube from the common duct. In no instance should the catheter be removed before the seventh postoperative day [5e] because of the danger of spillage of intestinal contents if the tract is not sufficiently walled off. There is a surprisingly small amount of drainage from the sinus after the removal of the catheter in the majority of cases. The average duration of drainage from the fistula in the present series was 2.6 days, including all cases. In 51% of all cases the drainage lasted less than 24 hours and in 67% less than 48 hours. The longest period of drainage in this series was 30 days.

The suture-closure method generally used in this study was described by Graham [6] and consists of interrupted sutures tied over a portion of omentum to close the perforation. The abdomen is closed with or without drainage. Ordinarily, continuous nasogastric suction is employed until active peristalsis is noted.

FACTORS INFLUENCING PROGNOSIS OF ACUTE GASTRODUODENAL PERFORATIONS

Most writers agree that the mortality rate for acute perforated ulcers increases with the age of the patient, the duration of the perforation before treatment, and

6. Graham, R. R.: Treatment of Perforated Gastro-Duodenal Ulcers, Surg., Gynec. & Obst. **64**:235-238 (Feb.) 1937.

the size of the perforation.[7] Also, the mortality is considered to be greater in women than in men.[8] Comparisons between the two methods under study in this paper are valid because these factors influencing prognosis of a perforated ulcer are nearly the same in each series. The comparisons are summarized in Table 1. Table 2 gives in detail the comparative time element between perforation and surgery for the two methods of treatment.

Since the factors considered to be the most important in affecting mortality for acute perforated ulcers are comparable in the two groups under study, it is felt that it is justifiable to draw conclusions based on the analysis in this study.

FINDINGS

A total of 165 acute perforations of gastroduodenal ulcers was obtained, with an over-all number of deaths of 23, or 13.9%. The mortality rates for the operative

TABLE 1.—*Comparison of Factors Influencing Mortality in the Mushroom-Catheter Group and the Suture-Closure Group (Graham)*

	Average Age of Patient	Sex	Location	Average Duration of Perforation	Average Size of Perforation
Suture-closure group (104 cases)	48.9 yr.	16% women	38% gastric	13.7 hr.	4.8 mm.
Mushroom-catheter group (44 cases)	49.2 yr.	18% women	43% gastric	13.5 hr.	6.5 mm.

TABLE 2.—*Comparison of Time Element Between Perforation and Operation for the Mushroom-Catheter and the Graham-Treated Groups of Perforations*

	Number of Cases		Deaths		Mortality	
Duration of Perforation	Mushroom-Catheter Group	Suture-Closure Group	Mushroom-Catheter Group	Suture-Closure Group	Mushroom-Catheter Group, %	Suture-Closure Group, %
0-6 hr.	18	52	1	0	5.5	0
7-12 hr.	13	27	1	2	7.6	7.4
13-24 hr.	6	10	2	1	33.3	10.0
25-48 hr.	2	5	0	1	0	20.0
Over 48 hr.	2	3	2	2	100.0	66.6

and nonoperative cases are contained in Table 3. The nine patients who were not operated on were given the wrong diagnosis or were in such poor general condition that surgery could not be carried out.

Table 3 also shows the mortality rates with the different methods of surgical treatment. It is noted that the mortality with the mushroom-catheter method is more than twice that for the series treated by primary suture closure.

7. (*a*) Baritell, A.: Perforated Gastro-Duodenal Ulcers, Surgery **21**:24-33 (Jan.) 1947. (*b*) DeBakey, M.: Acute Perforated Gastro-Duodenal Ulceration, ibid. **8**:852-884 (Nov.) 1940; Acute Perforated Gastro-Duodenal Ulceration, ibid. **8**:1028-1076 (Dec.) 1940. (*c*) Moore, S. W.: Late Results in Acute Perforation of Peptic Ulcer, S. Clin. North America **30**:429-441 (April) 1950. (*d*) Olson, H. B., and Norgore, M.: Perforated Gastro-Duodenal Ulcers, Ann. Surg. **124**:479-491 (Sept.) 1946. Turner.[4] Anderson and others.[5a]

8. DeBakey, M., and Odom, C. B.: Significant Factors in Prognosis and Mortality of Perforated Peptic Ulcer, South. Surgeon **9**:425-436 (June) 1940.

ANALYSIS OF DEATHS OCCURRING WITH THE MUSHROOM-CATHETER METHOD

Of the six deaths in the group of acute gastroduodenal perforations treated by the mushroom-catheter method, two were not related to the method, one was equivocal, and three were specifically related to the mushroom-catheter method.

The first death occurred in a 62-year-old man who had been bedridden for several weeks with a large retroperitoneal sympathoblastoma. He suffered a perforated ulcer while in the hospital and was operated on within six hours. He died 36 hours after surgery. With his general poor condition, this death can hardly be related to the mushroom-catheter method of treating the acute perforation.

The second death with the mushroom-catheter method occurred in an 80-year-old man who was being treated for infectious hepatitis in the hospital at the time of the perforation. He was operated on within 24 hours and died on the 12th postoperative day. He was markedly icteric at the time of perforation, and the amount of liver damage present was thought to be the main factor in his death rather than the method by which the perforation was treated.

TABLE 3.—*Mortality in Relation to Method of Treatment*

	Cases	Deaths	Mortality, %
Surgical treatment	156	14	8.9
Suture-closure method (Graham)	104	6	5.7
Mushroom-catheter method	44	6	13.6
Suture-closure and posterior gastroenterostomy	4	1	25.0
Drainage (perforation not found at surgery)	3	1	33.3
Gastric resection	1	0	0
Nonsurgical treatment	9	9	100.0
Total cases	165	23	13.9

The third death was that of a 58-year-old woman whose ulcer had been perforated 72 hours before operation. A large perforation 1.5 cm. in diameter was found. There was diffuse peritonitis. A catheter was placed in the perforation. Drains were left in the right flank and in the suprapubic region. She died on the third postoperative day of overwhelming peritonitis. Whether or not this death is related to the catheter method is equivocal because a postmortem examination was not performed and it is not known if a leak occurred around the catheter.

The fourth death in the mushroom-catheter group was that of a 64-year-old man whose ulcer had been perforated six and a half hours. The perforation was 5 mm. in diameter. A catheter was placed in the perforation. He died on the third postoperative day of peritonitis secondary to a leak of intestinal contents around the catheter into the free peritoneal cavity as demonstrated at postmortem examination. The fatal outcome in this case is specifically related to the mushroom-catheter method of treating the acute perforation since the perforation continued to leak after definitive treatment.

The fifth death occurred in a 68-year-old man whose ulcer had been perforated for 24 hours. He had a perforation which was 10 mm. in diameter in the pyloric region of the stomach. A mushroom catheter was placed in the perforation. The catheter was removed on the 19th postoperative day. In the meantime, gastric juices had been draining around the catheter, causing digestion of the abdominal wall.

After removal of the catheter, the fistula continued to drain profusely and the patient died in an emaciated condition 30 days postoperatively. In this case the perforation was larger than one for which the mushroom catheter technic is indicated, which may have played a part in the establishment of a permanent fistula. Another factor, however, is the length of time the catheter was left in place. Ordinarily, it is removed between the 10th and 13th postoperative days. The longer the catheter remains in place, the more definite is the establishment of a fistulous tract. While it is true that the proper technic of the mushroom-catheter method was not strictly adhered to in this case, it is felt that a fistula would not have occurred had the patient been treated by the suture-closure technic and a satisfactory outcome would have been obtained. This death is directly related to the mushroom-catheter method.

The sixth death in the mushroom-catheter group occurred in a 60-year-old man who had a perforated ulcer of 72 hours' duration prior to operation. The perforation was in the first portion of the duodenum and was 20 mm. in diameter. A catheter was placed in the perforation, and omentum was sutured around it to the bowel wall. On the fifth postoperative day duodenal contents began draining around the catheter, which continued until it was removed on the 10th postoperative day. After removal of the catheter, drainage was profuse, with digestion of the anterior abdominal wall. An anterior gastrojejunostomy was done on the 11th postoperative day. A nasogastric tube was introduced into the distal loop of jejunum through the gastrojejunostomy opening for the purpose of feeding the patient. The patient died on the day after the gastrojejunostomy. The use of the mushroom-catheter method in this case was contraindicated because of the large size of the perforation. The prognosis was also poor because of the long duration of the perforation before surgery was done. In this case, as in the previous one, had the perforation been treated by the suture-closure technic, a fistula would probably have been avoided. It is likely that recovery would have ensued had not a profusely draining duodenal fistula been superimposed on an already seriously ill patient. This death is related to the mushroom-catheter method.

Of these six deaths occurring in the group of perforations treated by the mushroom-catheter technic, therefore, the first two discussed may be disregarded as not being related to the method of treatment. The third death is equivocal. In each of the three remaining deaths, the use of the catheter method was related to the cause of death. Thus, three deaths, and perhaps four, in a group of 44 patients treated by the mushroom-catheter method occurred as a direct result of the use of the method, representing a mortality of at least 6.8% which probably would have been avoided by the use of the suture-closure technic.

ANALYSIS OF DEATHS OCCURRING WITH THE SUTURE-CLOSURE METHOD OF GRAHAM

Of the six deaths occurring in the group of perforations treated by the suture-closure method, five were not related to the method, while one was specifically related to the method.

The first death occurred in a 73-year-old man who was in the hospital under treatment for primary carcinoma of the liver. He had a preexisting iliac-vein thrombosis at the time of the ulcer perforation. His general condition was poor,

and he died on the eighth postoperative day of a pulmonary embolus. This death is not related to the method of treatment used for the perforation.

The second death occurred in a 50-year-old woman with a perforation of eight hours' duration. There was no history of previous gastrointestinal hemorrhage. The perforation was sutured and covered with a tag of omentum. The patient did well until the seventh postoperative day, when hematemesis and melena developed. She was treated conservatively with sedation, rest, and blood transfusions. The bleeding was not controlled, and on the 13th postoperative day a gastric resection was done. Despite adequate whole blood transfusions, the patient died five hours after the resection. This death is not related to the suture-closure method of treating the perforation.

The third death occurred in a 41-year-old man whose ulcer had been perforated 18 hours prior to surgery. He entered the hospital in profound shock and in a semicomatose condition. No blood pressure or pulse was obtainable on his admission. Plasma was given, and he was taken to surgery. No blood pressure or pulse was obtainable during the operation. A 3-mm. perforation was closed. The patient remained in shock for 24 hours. He never regained consciousness after surgery, was incontinent of urine and died on the eighth postoperative day. This death was due to severe brain damage secondary to prolonged shock with resultant cerebral anoxia and is not related to the suture-closure method of treating the acute perforation.

The fourth death in this group was that of an 88-year-old man whose ulcer had been perforated six days before surgical intervention was undertaken. He was comatose on his admission to the hospital, and no blood pressure could be obtained. His perforation was closed with the use of local anesthesia shortly after his admission. He did not respond at any time and died on the first postoperative day. The long duration of the perforation and the moribund condition on admission indicate an almost hopeless prognosis no matter what the method of treatment in this case. This death is not related to the suture-closure method.

The fifth death was that of a 57-year-old man with a perforated ulcer of 24 hours' duration. At surgery he was found to have a 20-mm. perforation of the posterior wall of the stomach. He died on the second postoperative day of peritonitis. This death is due to an overwhelming established infection and is not related to the suture method.

The sixth death in this group was that of a 49-year-old man whose ulcer had been perforated eight days before the time of surgical intervention. His disease was complicated by dementia paralytica, which made the diagnosis more difficult than usual. He had multiple perforations of the duodenum and pylorus, with considerable necrosis of the tissue. An attempt was made to seal off and cover the perforations with live omentum. He died of peritonitis on the eighth postoperative day. At autopsy he was found to have an open ulcer at the pylorus. This case represents a failure of the suture method, since the perforation continued to leak after definitive therapy.

Of the six deaths, then, one may be attributed to a failure of the suture-closure method. Among the 104 patients treated by suture closure, this one death represents a mortality rate of 0.9% in which the method was directly related to the cause of death.

This figure of 0.9% failure with suture closure is to be compared with the 6.8% failure obtained with the mushroom-catheter method.

COMPLICATIONS

The incidence of complications with both methods is similar except for the development of duodenal fistula. The incidence of duodenal fistula occurring in the 156 operative cases is 1.9%, which is a figure similar to that found by others.[9] However, the incidence of duodenal fistula with the mushroom-catheter method is five times greater than it is with the suture-closure method, as shown in Table 4. Two duodenal fistulas developed in the group treated by the mushroom-catheter method, and each resulted in a fatality, representing one-third of the deaths of the mushroom-catheter group. This is a significant and serious complication of the mushroom-catheter method.

MORBIDITY

The average length of time in the hospital for the perforations treated by the suture-closure method was 13.7 days. The average hospital stay for the mushroom-catheter group was 15.8 days. These figures represent a 15% longer period of

TABLE 4.—*Complications Occurring with the Mushroom-Catheter and the Suture-Closure Method*

	Catheter Method	Suture Method
Duodenal fistula	2 (4.5%)	1 (0.9%)
Wound infection	2 (4.5%)	1 (0.9%)
Evisceration of wound	1 (2.2%)	5 (4.7%)
Intraperitoneal abscess	1 (2.2%)	1 (0.9%)

convalescence for the perforations treated by the mushroom-catheter method. This longer hospital stay for the catheter-treated patients is due to delay until the catheter is removed on about the 10th or 12th postoperative day. Patients treated by the suture-closure method are usually able to leave the hospital on the seventh or eighth postoperative day, after removal of the skin sutures.

LATE FOLLOW-UP RESULTS

As has been reported by others,[10] it was found that survival of a patient with perforation of an ulcer does not offer any immunity against future ulcer complications. On the contrary, the development of a perforation indicates the gravity of the ulcer diathesis and forecasts further distress with ulcer in the majority of cases. A comparison of the follow-up of the patients treated by the mushroom-catheter method with that of the patients treated by the suture-closure method was made and, as might be expected, showed no significant differences.

9. McElhinney, W. T., and Holzer, C. E., Jr.: Factors Influencing Mortality from Acute Perforated Ulcer, Surg., Gynec. & Obst. **87**:85-92 (July) 1948. McCabe and Mersheimer.[5c]

10. Turner, F. P.: Acute Perforations of Stomach, Duodenum and Jejunum, Surg., Gynec. & Obst. **92**:281-295 (March) 1951. Werbel, E. W.; Kozoll, D. D., and Meyer, K. A.: Surgical Sequelae Following Recovery from Perforated Peptic Ulcer, S. Clin. North America **27**:93-108 (Feb.) 1947. Moore.[7c]

COMMENT

The mushroom-catheter method was not as satisfactory as the suture-closure method for treating acute perforations because it carried a greater mortality, a higher incidence of serious complications, and a greater morbidity. In addition the former method has the disadvantage of limited applicability. It is contraindicated in perforations larger than the size of a No. 16 mushroom catheter. The catheter must be made to fit snugly in the perforation, and live omentum must be sutured around it. A violation of any one of these principles may lead to serious or fatal peritonitis or to duodenal fistula.

The suture-closure method had the advantages of wide applicability and simplicity of technic. There are fewer possibilities of surgical error, fewer serious complications, and fewer deaths with suture closure.

SUMMARY

A series of 165 acute gastroduodenal perforations are reported, with an over-all mortality rate of 13.9%. One hundred and fifty-six perforations were operated on, with a mortality rate of 8.9%. The mortality in 104 patients with perforations treated by primary suture and closure was 5.7%. The mortality in 44 patients with perforation treated by the placement of a mushroom catheter into the perforation was 13.6%. Of six deaths in 104 patients treated by the Graham suture-closure method, one was directly related to the suture-closure method of treatment, an incidence of 0.9%. Of six deaths in 44 patients treated by the mushroom-catheter technic, three were directly related to the mushroom-catheter method of treatment, an incidence of 6.8%.

The incidence of complications in each group was approximately the same except for that of duodenal fistula, which occurred in 0.9% of the patients treated by suture closure and in 4.5% of the patients treated by mushroom catheter.

The hospital stay was 15% longer for the patients treated by mushroom catheter.

Late follow-up studies reveal no difference for the two groups. Neither method offers long-term cure, as the ulcer diathesis remains unaltered.

The mushroom-catheter method has the advantage of more comfort to the patient because a nasogastric tube is unnecessary.

CONCLUSION

The mushroom-catheter method of treating acute gastroduodenal perforations is less satisfactory than the suture-closure method of Graham.

Case Reports

TRAUMATIC RUPTURE OF THE BODY OF THE PSOAS MUSCLE

EUGENE A. GASTON, M.D.
FRAMINGHAM, MASS.
AND
WILLIAM C. WIGGLESWORTH, M.D.
BOSTON

TRAUMATIC rupture of the body of the psoas muscle has been known for centuries, the first recorded case having been reported by Galen, who observed the injury in a Roman gladiator.[1] Despite this fact, relatively few cases are recorded in the medical literature and the clinical picture, which is characteristic, is not widely known. To the uninitiated the symptom complex is confusing, and the resulting errors in diagnosis may lead to unnecessary operations and to avoidable deformities. The purpose of this paper is to report a case in which this unusual accident occurred and to emphasize the diagnostic pitfalls that were encountered.

REPORT OF A CASE

A 15-year-old white schoolboy was admitted to the Framingham Union Hospital on April 1, 1947, complaining of pain in the right hip. Ten days prior to his admission he noted the onset of an intermittent, mild, aching sensation in the right groin. At first no history of trauma could be obtained, but on close questioning the patient later recalled that on the day before the onset of symptoms, while he was playing football, his feet had been knocked from under him and forcible flexion at the hips had resulted from an effort to prevent a backward fall. At this time there was momentary discomfort in the region of the right hip and groin, but this did not disable him and he continued playing the game. On the day after the onset of symptoms, after a long ride in an automobile, it was noted that extension of the right hip caused an increase in the discomfort. Because of this he walked on the toes of his right foot, thereby keeping the hip flexed. On the advice of his family physician, much of the next three days was spent in bed, and during this time the discomfort progressively diminished until it was practically gone.

During the evening of the fifth day before admission, while the patient was lying in bed, the leg suddenly "went dead," and he was unable to move it for several minutes. At the same time recurrence of pain in the right hip and numbness over the anterior aspect of the thigh were noted. These symptoms gradually subsided within the next two or three hours. During the following three days, he suffered several similar episodes, with each of which the return of sensation was less complete and the pain around the hip joint severer. On the day before admission the pain became constant and much severer so that, for the first time, he was unable to sleep. On the day of admission he was unable to get out of bed because of weakness of the leg which "went out from under him" and was associated with a severe exacerbation of hip pain. From the onset

From the Surgical Service of the Framingham Union Hospital and the Department of Surgery of the Boston University School of Medicine.

1. Maydl, K.: Deutsche Ztschr. Chir. **17**:306, **17**:513, **18**:35, 1882.

of symptoms, the patient noted that flexion of the hip gave partial or complete relief of pain, but three days before admission progressively increasing degrees of flexion were necessary for relief. There was no history of chills, fever, or abnormal sweating.

The past history was of interest because, at the age of 4, extensive and prolonged bleeding had followed a minor laceration. Although a maternal uncle had died of "hemorrhage" and a brother was said to have a marked bleeding tendency, a diagnosis of hemophilia or other blood dyscrasia had never been established.

Physical examination revealed a well-developed, but rather poorly nourished, white boy who was lying quietly in bed with the right thigh held in a position of flexion. The positive physical findings were limited to the abdomen and the right lower extremity. The abdomen was difficult to examine because the patient relaxed poorly. The degree of muscular tension was somewhat greater in the right lower quadrant, and there seemed to be some tenderness in this region, but no masses were felt and there was no tenderness of the costovertebral angle. The right leg was flexed 90 degrees at the hip. Motions of the ankle and knee were within normal limits. Passive

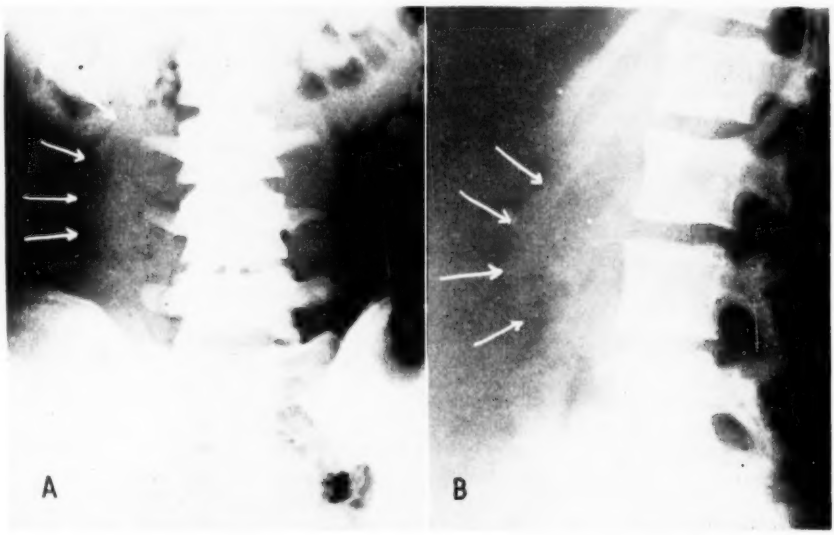


Fig. 1.—*A*, anteroposterior view of the abdomen showing abnormal outline of the right psoas shadow. *B*, anterior bulging of right psoas shadow in lateral view of abdomen.

adduction and flexion of the hip were normal and caused no pain. Extension and internal or external rotation of the hip caused extreme pain over the posterior surface of the hip joint. There was marked tenderness over the posterior aspect of the hip and on the medial and lateral surfaces of the thigh. The quadriceps femoris muscles were moderately atrophied. An area of anesthesia was noted over the anterior surface of the right thigh, extending downward over the medial aspect of the lower leg to a point just above the medial malleolus. The right knee jerk was diminished, while the other deep tendon reflexes were within normal limits.

The red blood cell count was 4,750,000, and the hemoglobin content was 16.5 gm. per 100 cc. The white blood cell count was 9,600, with 84% segmented forms. The cells and platelets appeared normal in the stained smear. The urine showed no abnormalities. The bleeding time was 2 min. 15 sec. and the clotting time 2 min. 29 sec., with normal clot retraction and the prothrombin time 95% of normal. The maximum, corrected sedimentation rate was 2.1 mm. per minute, and the reaction to the Hinton test was negative. Roentgenograms of the chest, pelvis and right hip showed no abnormalities.

During the first week of hospitalization the temperature followed a septic course, ranging from 98.6 to 103.4 F., and the white blood cell count became elevated to 16,000. Pain in the region of the right hip was sufficient to require narcotics for its relief. Because of severe pain and flexion contracture of the hip together with spiking fever and a high leucocyte count, a preliminary diagnosis of acute septic coxitis was made. During this time skin traction applied to the leg partially relieved the flexion deformity of the hip but gave no relief of pain. Penicillin was administered in doses of 400,000 units daily, without benefit. Because of failure to improve on conservative treatment, the right hip joint was explored through a posterolateral incision on the sixth hospital day. No evidence of pathologic changes could be demonstrated in or around the hip joint, and a culture of joint fluid was later reported to show no growth. This operation was followed by prolonged bleeding from deep in the wound, which was eventually controlled by packing. Appropriate blood studies failed to reveal evidence of hemophilia, or other blood dyscrasia, to account for the bleeding.

Three days after the operation, pain and tenderness became severer in the right lower quadrant of the abdomen and in the flank, and, for the first time, a mass became palpable in this region. The mass was ovoid, about 10 cm. in greatest diameter and extended from McBurney's point laterally and superiorly to the anterior axillary line. Roentgenograms of the abdomen done at this time revealed enlargement of the right psoas shadow (Fig. 1). Because of these findings, an exploratory operation was performed on the following day through a right flank incision. The unopened peritoneum was retracted medially, and a large, partially organized hematoma was found in the retroperitoneal space. It was surrounded by unorganized blood clot of recent origin. The clot and portions of the organizing hematoma were removed, revealing the frayed ends of the partially divided psoas muscle. Nerve trunks of the lumbar plexus were seen within the muscle defect. The muscle was extremely friable, and no attempt was made to repair it. A rubber tissue drain was inserted, and the wound was closed.

After the second operation there was rapid and progressive improvement so that, at the time of discharge from the hospital on the 19th postoperative day, all the pain had disappeared and the anesthetic areas over the thigh and the lower leg were largely gone. The only residual was a 45-degree flexion deformity of the hip, which completely disappeared with physical therapy during the following month. At present, the patient is completely well.

COMMENT

The cases of psoas rupture reported in the literature have in most instances followed physical exertion, usually involving a backward fall with a violent effort to regain balance by contraction of the flexors of the trunk. Of the 13 cases collected by Strandell,[2] only three were not produced in this manner. Two of these followed the severe convulsions of tetanus, and one resulted from "partus." Although muscle rupture is one of the recognized complications of electroshock therapy,[3] injury to the psoas muscle from this cause has not been reported.

The clinical picture can be conveniently divided into (*a*) local symptoms due to the muscle rupture itself; (*b*) symptoms caused by irritation of the nerves of the lumbar plexus; (*c*) abdominal symptoms, and (*d*) general symptoms.

The local symptoms consist of a mild to moderately severe pain, poorly localized to the region of the hip, thigh or lower back. This pain, which is due to the actual tearing of the muscle fibers, comes on at the time of injury, usually persists for only a short time and then either greatly improves or completely disappears. Patients

2. Strandell, G.: Acta chir. scandinav. **86**:149, 1942.

3. Savitsky, N., and Karliner, W.: Rupture of the Rectus Abdominis Muscle Following Electroshock Therapy, J. A. M. A. **143**:431 (June 3) 1950.

injured during athletic contets are often able to continue playing. This asymptomatic period is characteristic, and when a patient is seen during this interval the extent of the injury may be grossly underestimated.

The symptoms produced by irritation of the nerves of the lumbar plexus make their appearance from a few hours to several days after the initial injury and are of great importance in establishing the diagnosis. Evidently the nerves are seldom damaged by the initial injury. However, as the hematoma enlarges, they are subjected to abnormal stresses, and the resulting irritation gives rise to pain, to areas of paresthesia and anesthesia of the thigh and leg, and to muscle atrophy. The distribution and intensity of these symptoms will depend on the nerves involved and on the degree of irritation to which they are subjected. It is to be noted that pain in the hip joint, undoubtedly resulting from irritation of the obturator nerve, is frequently the presenting symptom and may be of such severity that other symptoms are overshadowed. Abnormalities of sensation are usually present in some or all of the areas supplied by the sensory nerves of the lumbar plexus. Muscle atrophy frequently involves the quadriceps group supplied by the femoral nerve. This atrophy may develop with great rapidity and points up the importance of early diagnosis and treatment.

The abdominal symptoms result from the enlarging hematoma, which produces a tender mass in the lower abdomen. Irritation of the contiguous parietal peritoneum gives rise to increasing abdominal tenderness, muscle spasm and rebound tenderness. The clinical picture of intraperitoneal disease, particularly abscess due to appendicitis or sigmoid diverticulitis, may be closely simulated. The x-ray demonstration of abnormalities of the psoas shadow may be most helpful in establishing the true significance of the mass.

General symptoms, especially fever and leucocytosis, are nearly always present and are usually due to resorption of damaged muscle tissue and extravasated blood. The possibility of infection of the hematoma must, however, be entertained, for, of the nine cases collected by Strandell in which complications were listed, suppuration was noted in three. Of the five psoas hematomas resulting from hemophilia reported by Tallroth,[4] two became infected. This high incidence of infection is probably related to the concentration of lymph vessels and nodes in the psoas region.

The diagnosis of psoas rupture should not be difficult if the condition is kept in mind. The history of injury and its attendent mild pain followed by a relatively asymptomatic period of variable duration, and finally the onset of severe pain with clinical signs pointing to irritation of the nerves of the lumbar plexus, is characteristic of all the cases reported in the literature. Michelson [5] has emphasized the value of lateral deviation of the upper third of the ureter and the lower pole of the kidney, as shown by retrograde pyelography, in the diagnosis of this condition. Abnormalities of the psoas shadow as demonstrated in roentgenograms of the abdomen are frequently characteristic and will often make pyelography unnecessary. The frequency with which psoas rupture mimics acute intra-abdominal disease, particularly appendicitis and sigmoid diverticulitis, should be borne in mind. It should be especially noted that irritation of the obturator nerve may cause severe pain localized in the

4. Tallroth, A.: Acta chir. scandinav. **82**:1, 1939.

5. Michelson, E.: Syndrome of Trauma to the Psoas Muscle, Arch. Surg. **50**:77 (Feb.) 1945.

region of the hip joint. When this pain is associated with fever, leucocytosis and a flexion deformity of the hip, as is often the case, the clinical picture may be easily confused with that of acute coxitis.

The treatment of rupture of the psoas muscle is entirely surgical and consists of evacuation and drainage of the hematoma. Operation should be undertaken as soon as the diagnosis can be established so that hemorrhage can be controlled, flexion contractures prevented, and the amount of muscle necrosis and permanent nerve damage minimized. It is not necessary to suture the divided muscle. Excellent exposure of the injured area can be obtained by the extraperitoneal approach, the oblique lumboilioinguinal incision used to expose the kidney and ureter being very satisfactory for this purpose.

SUMMARY

A case of traumatic rupture of the psoas muscle is reported. The clinical picture, which is characteristic, is explained on an anatomical basis. The importance of early and adequate surgical treatment is emphasized.

ONE-STAGE ESOPHAGECTOMY IN PRESENCE OF MEDIASTINITIS

VICTOR P. SATINSKY, M.D.
AND
SAMUEL D. KRON, M.D.
PHILADELPHIA

AT THE present time, the generally accepted management of perforation of the esophagus at the site of a malignant process consists in simple drainage of the mediastinum and administration of antibiotics, with gastrostomy or jejunostomy. If the patient survives, the neoplasm is extirpated at a later date. With this method, despite encouraging individual reports,[1] the over-all mortality rate is still high, exceeding 60%.[2] Unfortunately, these references fail to indicate the separate mortality rates for the malignant and the nonmalignant cases; it would be reasonable to suppose that the mortality in the former group is higher.

In view of the advances made in thoracic surgery and anesthesia and the wider application of antibiotics, it appeared to us that primary resection for carcinoma of the esophagus associated with perforation and mediastinitis merited consideration. A search of the literature fails to reveal any reports recommending this procedure. We are, therefore, presenting a case successfully managed in this way.

REPORT OF A CASE

A 58-year-old white woman was admitted to Mount Sinai Hospital, Philadelphia, on May 9, 1948, complaining of difficulty in swallowing. The patient noted "heartburn" for one year and, during the five months prior to her admission, increasing epigastric and substernal discomfort on swallowing. Vomiting frequently afforded relief; the appetite was good. There was a weight loss of 5 lb. (2.3 kg.). A roentgenogram showed an obstructing lesion in the lower esophagus (Fig. 1 and 2). There were no abnormal physical findings. The blood pressure was 155/75, pulse rate 80 and regular, and the temperature 98.6 F. The hemoglobin content was 13 gm. (90%), and the white blood cell count 7,100 (71%).

Esophagoscopy (on May 11, 1949) revealed a fungating growth 2½ in. (6 cm.) from the gastric cardia, practically filling the esophageal lumen. The esophagoscopist stated that the lesion was friable and bled freely on touch and that the walls of the esophagus did not seem infiltrated or fixed. The esophagoscope was not passed beyond the lesion. A biopsy was made, and the pathologic report was adenocarcinoma.

The day after esophagoscopy the patient began to complain of considerable chest pain radiating along both subcostal regions. She appeared ill. The temperature was 103.5 F. and the pulse rate 120. Administration of crysticillin, 300,000 units every 12 hours, and streptomycin, ¼ grain (0.015 gm.) every six hours, was started. A Levine tube was passed and

From the Surgical Service No. II, Mount Sinai Hospital.

1. Adams, R.: Acute Suppurative Mediastinitis, J. Thoracic Surg. **15**:336-340 (Oct.) 1946. Dorsey, J. M.: Surgical Treatment of Perforation of Esophagus, Arch. Surg. **56**:24-33 (Jan.) 1948. Birgard, J. D., and Kerr, H. H.: Surgical Management of Instrumental Perforation of Esophagus, ibid. **58**:739-749 (June) 1949.

2. Jackson, C.: Diseases of Nose, Throat and Ear, Philadelphia, W. B. Saunders Company, 1945, p. 708.

Fig. 1.—Preoperative barium roentgenogram. Note filling defect in lower esophagus.

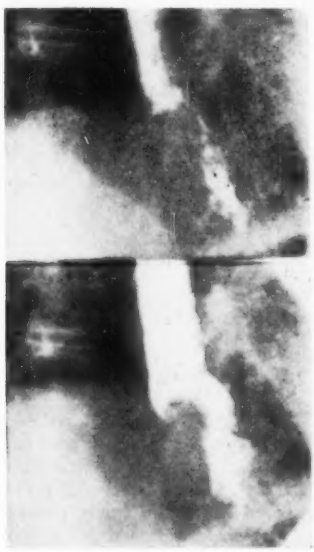


Fig. 2.—Spot films of filling defect.

suction applied. The temperature remained elevated. On May 13, 1949, the patient was subjected to operation. A resection of the esophagus, with supra-aortic esophagogastrostomy, was performed; closure of the chest was instituted, with mediastinal drainage.

The significant operative findings were as follows: A large amount of purulent fluid was present in the pleural cavity. The lung was covered with a thick fibropurulent exudate and was plastered over a perforation in the esophagus at the level of the neoplasm. The liver showed no gross metastases. There were no enlarged aortic nodes; a few enlarged nodes were present in the mediastinum.

The pathologic report on the specimen showed extensive primary stenosing adenocarcinoma of the esophagus involving all the coats of the wall, a traumatic perforation with resultant infection and marked necrotizing fibropurulent periesophagitis (Fig. 3). A biopsy of

Fig. 3.—Photomicrograph of esophagus showing area of suppuration and necrosis.

mediastinal pleura revealed necrotizing fibrinous pleuritis. There was no metastasis in the excised nodes.

Postoperative treatment consisted primarily of intravenous administration of fluids, penicillin, and streptomycin. Feedings through the Levine tube were started on the second postoperative day. Oral liquids were started on the eighth postoperative day, and the Levine tube was removed on the ninth day. The diet was then gradually increased. On the thirteenth postoperative day radiopaque oil was inserted through a catheter into the esophagus. There was no obstruction to flow or leakage at the anastomosis. During the early postoperative period, the temperature sporadically rose to 100 or 101 F.; this rise repeatedly responded to administration of aureomycin or chloramphenicol (chloromycetin®) but not to penicillin. The patient was discharged on June 27, 1949, comfortable, eating well, and afebrile. At the time of this writing, two years after esophagectomy, she is in good health, asymptomatic, and maintains an immediate postoperative weight gain of 12 lb. (5.4 kg.).

COMMENT

The impulse to manage this case by the usual method of mediastinotomy, gastrostomy, and secondary esophagectomy was superseded by a consideration of the many advantages coincident to primary resection. These advantages may be listed as follows:

1. Troublesome gastrostomy feedings are obviated.

2. Esophagectomy is technically easier if gastrostomy and jejunostomy have not been performed.

3. Long-standing mediastinitis with its attending adhesion formation and associated fibrothorax is avoided.

4. Decortication of the lung is simplified if performed at an early date and may not even be necessary.

5. The dangers of a secondary operation, anesthetic as well as surgical, are prevented.

6. Patients with carcinoma of the esophagus do not appear to do well with draining mediastinal wounds.

7. The period of hospitalization and convalescence is significantly reduced.

8. The malignant growth is removed immediately, and seeding in and about the pleural space is thereby greatly minimized. Roberts suggests "that it is unlikely that carcinoma cells will be seeded in the presence of mediastinitis," noting that "tissue transplants" do not fare well in the presence of an infection.[3] Conceivably, once the mediastinitis subsides, seeded malignant cells might "take," hence the urgency for extirpation.

SUMMARY AND CONCLUSIONS

A case of perforation of carcinoma of the esophagus caused by instrumentation and associated with marked mediastinitis is presented. The treatment instituted was a one-stage esophagectomy, primary decortication of the lung, and concomitant drainage of the mediastinum. Peritonitis did not result from the communication of the thoracic with the abdominal cavity. As anticipated, antibiotics prevented this complication, just as it enabled the successful completion of esophagectomy in the presence of mediastinitis. The advantages of this method of management are outlined.

3. Roberts, M. S.: Personal communication to the authors.

LIPOMA OF ILEUM WITH INTUSSUSCEPTION AND CARCINOMA OF CECUM

KENNETH C. SAWYER, M.D.
ALEXIS E. LUBCHENCO, M.D.
DENVER
AND
M. J. STEWART, M.D.
LOVELAND, COLO.

LIPOMA of the ileum is a comparatively rare clinical condition. Such a lesion accompanied with carcinoma of the cecum in the same patient is extremely rare. At operation the patient to be reported on was found to have the above two entirely separate tumors in addition to an ileocolic intussusception, making an interesting and unusual case.

On reviewing the literature, including reports of Stetten,[1] Saint,[2] Schottenfeld,[3] and Cavanaugh,[4] one is impressed with the comparative infrequency of clinical lipomas in the gastrointestinal tract although a fair number of subclinical lipomas have been noted at postmortem examination.[5] More of the tumors have been found in the colon than elsewhere in the gastrointestinal tract; those in the ileum are next in frequency and a few are located in the stomach and duodenum. Smith and Mayo [5b] found reports of 67 cases of small bowel lipomas in the Mayo Clinic files and noted that 53 were subclinical, found only at necropsy. In their nine cases in which the tumor produced symptoms, intussusception was "the event that generally led to the diagnosis of lipoma." There are two types, submucous and subserous, although the submucous type predominates in numbers by a wide margin.

REPORT OF CASE

Clinical History.—A 70-year-old white woman was referred to the hospital complaining of shortness of breath and a swollen abdomen. Although this patient had noted a lump in the right lower part of her abdomen for about five years, she had felt fairly well until a stuffy feeling developed in her chest about one month previously.

Her past history revealed that she had been married 47 years and had eight children living and well. She had a dislocation of the left hip at the age of 13, with stiffness since that time. She had undergone an uncomplicated appendectomy but nothing else of significance.

1. Stetten, D.: The Submucous Lipoma of the Gastrointestinal Tract: Report of Two Successfully Operated Cases and an Analysis of the Literature, Surg., Gynec. & Obst. **9**:156-176, 1909.

2. Saint, J. H.: Chronic Intussusception Due to Submucous Lipoma of Ascending Colon, Am. J. Surg. **58**:414-421, 1942.

3. Schottenfeld, L. E.: Lipomas of the Gastrointestinal Tract, Surgery **14**:47-74, 1943.

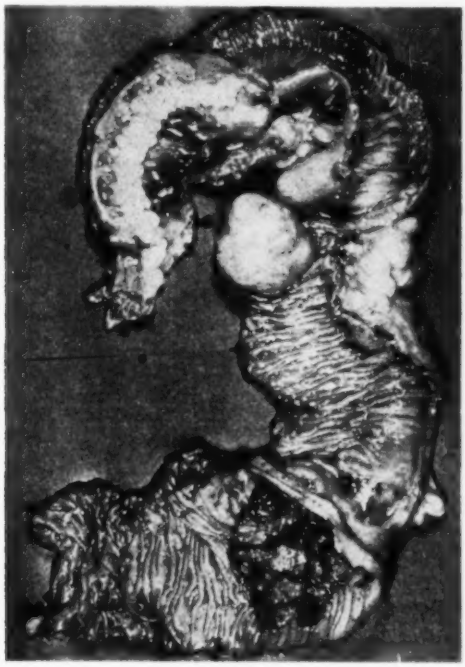
4. Cavanaugh, H. N.: Submucous Lipomas of the Large Bowel, Am. J. Surg. **7**:860-864, 1950.

5. (*a*) Comfort, M. W.: Submucous Lipomata of the Gastrointestinal Tract: Report of 28 Cases, Surg., Gynec. & Obst. **52**:101-118, 1931. (*b*) Smith, F. R., and Mayo, C. W.: Submucous Lipomas of the Small Intestine, Am. J. Surg. **7**:922-928, 1950.

The patient had noticed a gradual increase in the size of the abdominal mass. She found it necessary to take pills to keep her bowels moving. Except for some epigastric distress and dyspnea, there were no other significant symptoms or complaints.

Physical Findings.—On physical examination there was a soft systolic murmur present in the pulmonic area. A large, tender mass seemed to fill the entire right side of the abdomen. A healed right rectus scar was noted. There was definite ankylosis of the right hip joint. The blood pressure was 178/76, and the pulse was 92 and regular. The condition was otherwise essentially normal.

Laboratory Findings.—Blood counts, urinalysis, and chemical studies of the blood gave normal results. Cystoscopic examination with pyelography was normal except that a No. 4 F catheter was obstructed 5 cm. above the right ureteral orifice. X-ray examinations demonstrated marked



Photograph of the gross specimen showing a lipoma in the distal ileum and a carcinoma on the posterior wall of the cecum.

deformity of the left hip, probably secondary to old slipped epiphysis or injury. A barium enema showed what appeared to be an obstructing lesion at the hepatic flexure colon, with some distention of loops of small bowel. The abdominal viscera were displaced anteriorly and to the patient's left side.

Preoperative Impression.—A preoperative diagnosis was made of a large abdominal mass, probably retroperitoneal tumor.

Operation.—The abdomen was opened, and the distal ileum was found intussuscepted into the cecum. The head of the intussusception appeared to be an intraluminal mass. The mesentery proximal to this area was hemorrhagic. The intussusception was reduced without difficulty. A firm mass was palpable in the distal ileum and in the cecum. The parietal peritoneum was divided lateral to the cecum. The ileocolic right midcolic vessels were clamped, divided, and ligated, and about 80 cm. of the distal ileum, cecum, ascending colon and half of the transverse

colon were resected. All vessels were ligated and a primary, end-to-end ileotransverse colostomy was performed over a Rankin clamp. One layer of gastrointestinal suture and one cotton musculoserosal layer were used for the anastomosis. The anastomosis was reinforced with omental tags and fat. The mesentery was reconstructed. The pathologist opened the specimen in the operating room and discovered a large lipoma of the ileum. The mass in the cecum was a carcinoma. The abdomen was closed in layers with fine catgut and silk.

Pathologist's Findings.—Macroscopic Observations: The specimen (Figure) consisted of the cecum, ascending and transverse colon, and a segment of ileum. The cecum measured 21 cm. in length and presented in the cecal pouch a 7.5 by 5 cm. polypoid tumor which was ulcerated centrally (one section border of tumor). Multiple sections through regional lymph nodes revealed that they ranged between 5 and 15 mm. in diameter. Six of these were sectioned. Two of them contained metastatic carcinoma. The 48-cm. section of ileum presented 25 to 30 cm. proximal to the ileocecal valve an obstructing soft tumor mass 6 cm. in diameter. At this point the bowel presented partial intussusception. When the ileum was opened, an intraluminal, soft, well-demarcated tumor mass covered by thin but intact mucosa was demonstrable. This tumor measured 6 by 4.5 by 4.5 cm. On section it consisted of a firm, golden yellow, fatty material.

Microscopic Observations: The lesion of the cecum presented irregular adenocarcinomatous elements which extended throughout the entire thickness of the bowel wall. Some of the regional mesenteric lymph nodes were subtotally replaced with metastatic cancer. The submucosal lesion from the ileum consisted of adult fat cells. Sections included overlying mucosa with the smooth muscle of its wall being compressed against the submucosa, causing almost complete obliteration of the mucosa muscularis and the submucosa.

Diagnosis.—The diagnosis was (1) adenocarcinoma of the colon, in the cecal region, (2) adenocarcinoma, metastatic, of regional mesenteric lymph nodes, (3) lipoma of the wall of the ileum, with (4) secondary partial obstruction of the ileum. The convalescence was uneventful, and the patient was discharged from the hospital on the 22d postoperative day. She has remained well since.

SUMMARY

A brief discussion of lipoma of the ileum has been presented. There follows the case history of a patient with lipoma of the ileum complicated by ileocolic intussusception and a carcinoma of the cecum, a rare combination of clinical entities.

CORRECTION

In the article by Drs. D. Emerick Szilagyi, Gilbert D. Jay III and Edward R. Munnell, published in the October, 1951, issue, page 435, Dr. Edward R. Munnell's name was incorrectly given as Edward D. Munnel.

CYST OF LUNG ASSOCIATED WITH ANOMALOUS PULMONARY ARTERY

CHARLES B. RIPSTEIN, M.D.
AND
GEORGE A. DEGENSHEIN, M.D.
BROOKLYN

ALTHOUGH anomalous pulmonary arteries have long been recognized,[1] the first description of such a vessel associated with sequestration of the lung is credited to the unpublished thesis of Fischer, cited by Müller in 1927.[2] In 1941 Haight [3] made brief reference to two cases, and others [4] have since described isolated instances of this anomaly. With an increasing number of thoracic operations, more material became available, and in 1946 Pryce [5] reported eight cases and reviewed the literature in detail.

There are several theories as to the origin of the vessel and the sequestrated mass of lung. Pryce [5a] has written extensively on the subject, and here only a brief mention is necessary. Embryologically the pulmonary artery develops in a vascular plexus which has connections with both dorsal and ventral aortae (Fig. 1). Because of embryonic shifts the connections to the dorsal aorta are normally disrupted. If there is a delay in shift or if the dorsal aorta captures a bulbous tip of the bronchial tree, the subsequent development is that of an anomalous artery, and this is usually associated with traction on the captured lung bud. If this vessel grows without disruption or sequestration, it remains merely an anomalous vessel entering a normal pulmonary lobe. If, however, the bulbous tip detaches from the lung bud, survives and grows, sequestration of an accessory lobe results in association with the anomalous vessel. This theory is satisfactory in that it explains the findings in reported cases. Thus the sequestration may be complete with an independent bronchus, or it may be incomplete, communicating with the adjacent lung. The incomplete type may be further subdivided into the extralobular, in which a fissure exists between normal and ectopic lung, and the intralobular, which is revealed only by the dissection of a separate bronchial tree to the sequestrated segment.

From the Department of Surgery, Maimonides Hospital, Brooklyn, and the State University of New York College of Medicine.

1. Taussing, H.: Congenital Malformations of the Heart, New York, The Commonwealth Fund, 1947.

2. Müller, L.: Über angeborene Atresia der rechten Pulmonalarterie bei einem Erwachsenen, Ztschr. Kreiseaufforsch. **19**:561, 1927.

3. Haight, C., in discussion on Brown, A. L., and Brock, W.: Method of Treatment of Large Pulmonary Air Cysts, J. Thoracic Surg. **11**:630, 1942.

4. Bruwer, A.; Claggett, O. T., and McDonald, R. J.: Anomalous Arteries to the Lung Associated with Congenital Pulmonary Abnormalities, J. Thoracic Surg. **19**:957, 1950. Douglass, R.: Anomalous Pulmonary Vessels, ibid. **17**:712, 1948.

5. (*a*) Pryce, D. M.: Lower Accessory Pulmonary Artery with Intralobular Sequestration, J. Path. & Bact. **58**:457, 1946. (*b*) Pryce, D. M.; Sellors, T. H., and Blair, L. G.: Intralobular Sequestration of Lung Associated with Abnormal Pulmonary Artery, Brit. J. Surg. **35**:18, 1947.

The anomalous vessels are pulmonic in origin, as evidenced by a large amount of elastic tissue in the wall. However, they carry oxygenated blood from the systemic circulation, and the intravascular pressure may be high. This leads to an increased incidence of arteriosclerosis. These vessels may arise from any portion of the thoracic or upper abdominal aorta. They may attach to normal lung, a sequestrated mass, or both. In one of the earliest cases reported [6] both lower lobes were supplied from a common trunk arising from the abdominal aorta, bifurcating within the peritoneal cavity and perforating each hemidiaphragm to supply the lower lobes. Such anomalies are usually associated with extralobular sequestration and often with a diaphragmatic hernia.

The importance of recognizing this anatomical complex is twofold. First, from a technical viewpoint, it can be dangerous to divide an unsuspected vessel near the diaphragm and have it retract to the aorta or into the abdomen. Findlay and Maier [7] refer to two cases [8] of fatal hemorrhage at operation after inadvertent division of such vessels. The diagnosis of cystic disease should place the surgeon on guard for

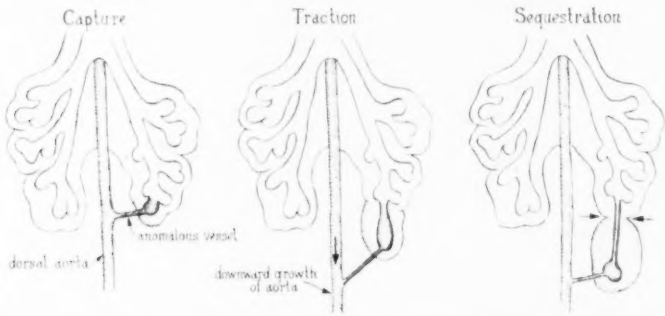


Fig. 1.—Illustration of the theory of development: "capture" of the lung bud by a disrupting plexus vessel from the dorsal aorta; traction due to caudad shift of the dorsal aorta; sequestration completed.

an anomalous vessel. Second, from the diagnostic viewpoint, many cases of lung cyst with secondary infection are treated medically because of failure of diagnosis. McGrath and Magnussen [9] have reported a series of 15 cases in which the primary diagnoses included empyema, pulmonary abscess, tuberculosis, tuberculous empyema, sarcoma, diaphragmatic hernia, and bronchiectasis. Many surgical procedures were carried out because of these mistaken diagnoses, one patient having undergone 15 operations with a diagnosis of empyema. These cases should be recognized early and the patient subjected to an adequate operation before ulceration and infection

6. Eppinger, H., and Schauenstein, W.: Krankheiten der Lungen, Ergebn. path. Anat. **8**:267, 1902.

7. Findlay, C. W., and Maier, H. C.: Anomalies of the Pulmonary Vessels and Their Surgical Significance, Surgery **29**:611, 1951.

8. Douglass, R.: Anomalous Pulmonary Vessels, J. Thoracic Surg. **17**:712, 1948. Harris, H. A., and Lewis, I.: Anomalies of the Lungs with Special Reference to the Danger of Abnormal Vessels in Lobectomy, ibid. **9**:666, 1940.

9. McGrath, E. T., and Magnussen, M. T.: Cystic Disease of the Lung, Arch. Surg. **57**:427 (Sept.) 1948.

of the adjacent lung occurs or the complications of hemorrhage, infection, pneumothorax, and hemothorax ensue.[10]

REPORT OF CASE

A. A., a white boy aged 16, was admitted to Maimonides Hospital on Aug. 10, 1950. This patient had reported to his physician after a routine roentgenogram of the chest when he was told that there were "spots in his lung."

For four and a half years the patient had noted frequent upper respiratory infections during the colder months. These infections were more persistent than the ordinary colds suffered by others in his family and were accompanied with cough and yellow purulent sputum. There was no dyspnea, hemoptysis, or weight loss. His last upper respiratory infection occurred two months before admission and on this occasion he was awakened frequently with spasms of coughing

Fig. 2.—Specimen showing main loculated cyst in the left lower lobe. Note ligated anomalous vessel entering posteromedial portion.

followed by expectoration. This episode, as the others, passed off, leaving the patient asymptomatic and able to carry on his usual school and home duties.

Physical examination showed a well developed hyposthenic young man. Auscultation of the chest revealed subcrepitant post-tussic rales at the left lung base. The remainder of the physical examination was essentially noncontributory.

Roentgenologic examination of the chest revealed multiple cystic areas in the left lower lobe (Fig. 2). There was one large cyst measuring 3 by 5 cm. at the level of the fifth rib and several smaller cysts inferiorly. The right lung was free from disease. The diagnosis was multiple congenital bronchial cysts confined to the left lower lobe.

10. Kloske, E.; Bemokin, A., and Parsownet, A. E: Cystic Disease of the Lung, Ann. Int. Med. **24**:217, 1946. Moersch, H. J., and Claggett, O. T.: Pulmonary Cysts, J. Thoracic Surg. **16**:179, 1947.

Left thoracotomy was performed on Aug. 12, 1950. At operation several saccular dilatations were felt in the posterior and medial aspects of the left lower lobe. An anomalous vessel was found passing from the aorta into the base of the left lower lobe between the leaves of the pulmonary ligament (Fig. 3). A left lower lobectomy was performed.

The postoperative course was uneventful. The thoracotomy drainage tube was removed in 48 hours, and the patient was discharged from hospital on the seventh postoperative day. He has subsequently returned to full activity and has no residual symptoms.

Pathological Findings.—Gross Examination: The specimen is that of a left lower lobe weighing 195 gm. Two soft grayish-black discrete nodes lie next to the bronchi. On the anterolateral aspect of the middle third of the pleura there are fibrous adhesions which extend inferiorly into the posterior medial border of the lobe. In this region an anomalous artery is found which measures 0.5 cm. in diameter. This artery sends branches to the base along the posterior medial border. Only the anterior branches are related to the large cyst. No connections can be found between the aberrant artery and the pulmonary artery and vein. Four centimeters from the proximal line of resection of the lower lobe bronchus another bronchus opens suddenly into a multisaccular cystic space occupying the entire posterior half of the specimen and extending from

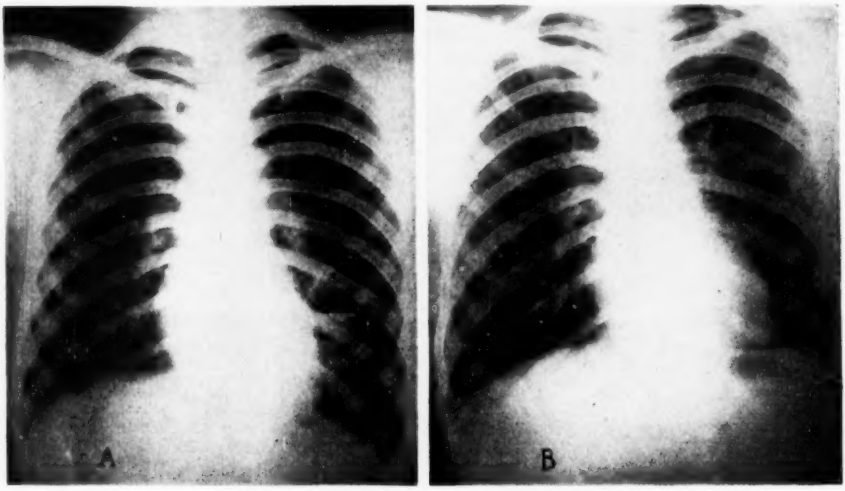


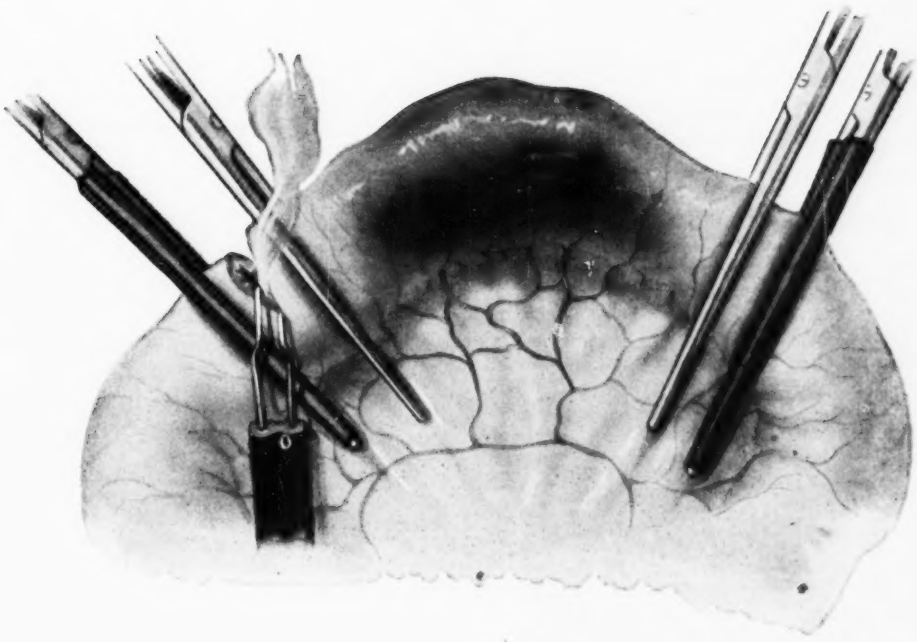
Fig. 3.—*A*, preoperative roentgenogram demonstrating large cyst with fluid level in the left lower lobe; *B*, roentgenogram taken six months after left lower lobectomy.

medial to lateral aspects. The approximate size of the cyst laid open is 10 by 7 cm. The cyst contains dirty yellow pus and is lined by a smooth glistening, yellowish gray membrane. There are several other smaller cysts in this same lobe.

Microscopic Examination: Hilar nodes show anthracosis. The bronchi reveal marked mononuclear infiltration in their walls throughout the lobe. The bronchial division leading into the cyst undergoes a transition from intact bronchial wall and cartilage into a layer of fibrous tissue partially covered with pseudostratified columnar epithelium. The cyst itself shows focal squamous lining, but for the most part the surface is merely fibrous tissue with neutrophils, eosinophils, and assorted mononuclear cells. At one point in the cyst wall there is abundant smooth muscle.

SUMMARY AND CONCLUSIONS

A case of anomalous pulmonary artery associated with intralobular sequestration and pulmonary cyst formation is reported, and a brief review of the pathogenesis of this anomaly is presented. This condition must be borne in mind to ensure accurate diagnosis and proper surgical therapy.



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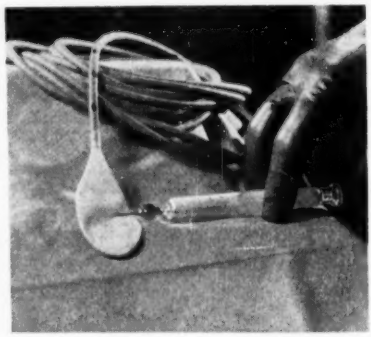

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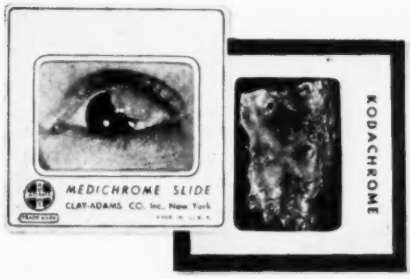

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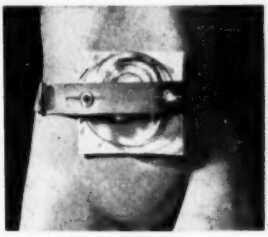

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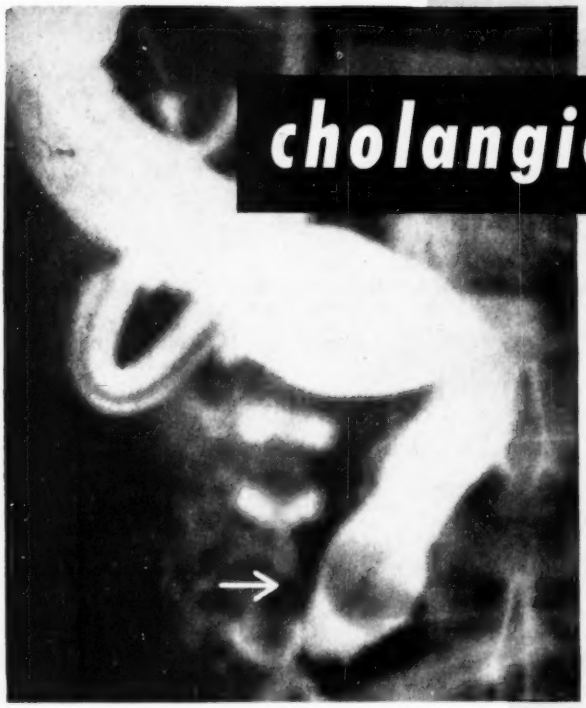

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1. Byrne, R. V.: Amer. Jour. Surg., 78:514, Oct., 1949.
2. Hicken, N. F., Stevenson, U. L., Franz, B.J., Crowder, Earl: Amer. Jour. Surg., 78:347, Sept., 1949.

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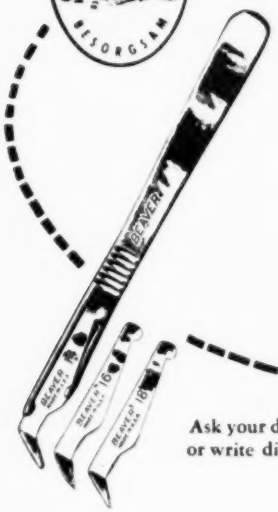

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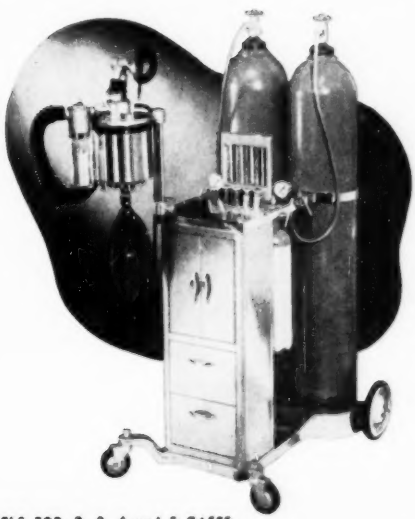

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